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EPIDEMIOLOGY, DIAGNOSIS AND TREATMENT OUTCOMES OF TUBERCULAR UVEITIS IN A SETTING OF HIGH HIV PREVALENCE

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A thesis submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of Doctor of Philosophy

Johannesburg 2 August 2022

DECLARATION

I, Hassan Dawood Alli declare that this thesis is my own work. It is being submitted for the degree of Doctor of Philosophy in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.



……

2 August 2022

DEDICATION

I dedicate this thesis to my late parents S. Dawood M. Alli and Miriam Alli.

To my wife Fairoz and children, Muhammad Yaaseen Alli, Muhammad Riyaad Alli and Nasreen Alli for their unwavering support.

PUBLICATIONS AND PRESENTATIONS ARISING FROM THIS THESIS

Publications

1. Alli HD, Ally N, Mayet I, Dangor Z, Madhi SA. Global Prevalence and Clinical Outcomes of Tubercular Uveitis: A Systematic Review and Meta-analysis. *Survey of Ophthalmology*. 2021. doi: 10.1016/j.survophthal.2021.10.001.

2. Alli HD, Ally N, Mayet I, Joseph L, Omar SV, Madhi SA. Tubercular Uveitis in Uveitis Cases in a High TB and HIV Setting: A Prospective Cohort Study. *Translational Vision Science and Technology*. 2022. doi.org/10.1167/tvst.11.1.9.

3. Alli HD, Ally N, Mayet I, Joseph L, Omar SV, Madhi SA. Treatment Outcome of Tubercular Uveitis in a High TB and HIV Setting: A Prospective Cohort Study. *Clinical Ophthalmology*. 2021;15:4839–4846. doi: 10.2147/OPHTH.S342268.

Presentations

1. Epidemiology and treatment outcomes of tubercular uveitis in a high HIV setting. 1st *Scientific Conference of the African Ophthalmology Council*, Virtual. October 2021

2. Epidemiology and treatment outcomes of tubercular uveitis in a high HIV setting. 2nd *Wits Ophthalmology Research Day*, Johannesburg, South Africa. November 2021

ABSTRACT

Introduction

The diagnosis of tubercular uveitis (TBU) is difficult. The lack of a diagnostic gold standard has contributed to challenges in determining the burden of TBU, clinical predictors of TBU, and deciding when to initiate anti-tubercular treatment (ATT). Another challenge is the duration of ATT required for resolution to be achieved. We evaluated the prevalence of TBU in adults presenting with uveitis, and delineated clinical features associated with TBU. Furthermore, we evaluated the time to resolution of inflammation in TBU cases on standard ATT. We also performed a systematic review and meta-analysis of TBU to estimate the global prevalence and treatment outcomes of TBU.

Methods

The systematic review and meta-analysis of TBU studies included studies published in PubMed, Scopus and EMBASE, up to 30 June 2020.

We conducted a prospective cohort study of adult uveitis cases to determine the prevalence of TBU and the clinical features associated with such cases. The diagnosis of TBU was made using a composite reference which included: i. any clinical signs of uveitis; ii. exclusion of other causes of uveitis; and iii. positive QFT-G, and/or TST, and/or TB PCR of aqueous or vitreous samples. TBU cases were treated with standard ATT (and corticosteroids) for 9 months and followed up to 15 months post-diagnosis and post-treatment-onset.

Results

The meta-analysis estimated that prevalence of TBU in 65607 uveitis cases was 4.0% [95% CI, 3-5]; including 7.0% [95% CI, 5-11] in countries with a high burden of TB; 11.0% [95% CI, 8-15] in sub-Saharan Africa; and 3.0% [95% CI, 2-4] in countries with a low burden of TB. The clinical response rate to treatment in the studies included in the meta-analysis was 82.0% [95% CI, 75-89].

In the longitudinal study undertaken at a single facility in Johannesburg, South Africa, 49 (62%) of 79 cases presenting with uveitis were diagnosed with TBU; there were 41 presumed and 8 confirmed TBU cases. Forty-three (54%), thirty-nine (50%) and eight (10%) cases had a positive TST, QFT-G and TB PCR, respectively Among the uveitis cases, there was higher odds of diagnosing TBU in those with chronic uveitis (OR:4.1, P=0.008) and female sex (odds ratio [OR]:5.1, P=0.002), whereas TBU was less likely associated with HIV sero-positive status (OR: 0.2, P=0.001). Choroidal granulomas (P=0.176) and serpiginous-like choroiditis (P=0.292) were more common in the TBU group, albeit not significantly. Using the multilevel mixed effects model (OR=1.21; 95% CI, 1.03-1.41; P=0.017) and generalized estimating equations (OR=1.21; 95% CI, 1.05-1.39; P=0.008), resolution was achieved at 6 months post-treatment-onset.

Conclusion

The prevalence of TBU in cases presenting with uveitis in our setting was higher than observed elsewhere, including previous studies from sub-Saharan Africa. Tubercular uveitis was associated with chronic uveitis and female sex, and less likely with HIV sero-positive status. Resolution of inflammation in TBU cases was achieved at 6 months post-treatment-onset, suggesting a minimum of 6 months ATT.

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ABBREVIATIONS

AIDS	Acquired immunodeficiency syndrome
ANA	Antinuclear antibodies
ANCA	Antineutrophil cytoplasmic antibodies
APMPPE	Acute posterior multifocal placoid pigment epitheliopathy
ARN	Acute retinal necrosis
ATP	Adenine triphosphate
ATT	Anti-tubercular treatment
BCG	Bacille-Calmette-Gue´rin
BRB	Blood-retinal barrier
CA	California
CDC	Centers for Disease Control and Prevention
CFP-10	Culture filtration protein 10
CFU	Colony forming units
CI	Confidence interval
CMV	Cytomegalovirus
COTS	Collaborative Ocular Tuberculosis Study
CSF	Cerebrospinal fluid
CT	Computed tomography
Ct	Cycle threshold
CTP	Cytosine triphosphate
DNA	Deoxyribonucleic acid
EBV	Epstein-Barr virus
EPTB	Extrapulmonary tuberculosis
ELISA	Enzyme linked immunosorbent assay
ESAT-6	Early secreted antigenic target 6
ESR	Erythrocyte sedimentation rate
FA	Fluorescein angigram
FBC	Full blood count
FHI	Fuchs heterochromic iridocyclitis
GBD	Global burden of disease
GTP	Guanine triphosphate
HBC	High-burden country
HREC	Human Research Ethics Committee
HHV6	Human herpes virus 6
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HSV	Herpes simplex virus
IGRA	Interferon-gamma release assay
INF-γ	Interferon-gamma
JIA	Juvenile idiopathic arthritis
JBI	Joanna Briggs Institute
LFT	Liver function test
LOD	Limit of detection
MEWDS	Multiple evanescent white dot syndrome
MGIT	Mycobacterial growth indicator tubes
Mtb	Mycobacterium tuberculosis
NICD	National Institute for Communicable Diseases

NRAMP1	Natural resistance-associated macrophage protein 1
NTBRL	National TB Reference Laboratory
NTM	Non-tuberculous mycobacteria
OCT	Optical coherence tomography
OPD	Outpatient Department
OR	Odds ratio
P	Probability
PIC	Punctate inner choroidopathy
PCR	Polymerase chain reaction
PLWH	People living with HIV
PORN	Progressive outer retinal necrosis
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PPD	Purified protein derivative
QFT	QuantiFERON
QFT-G	QuantiFERON Gold
RCF	Relative centrifugal force
REDCap	Research Electronic Data Capture
RIF	Rifampicin
RNA	Ribonucleic acid
ROC	Receiver operating characteristic
RPR	Rapid plasma reagin
RT-PCR	Reverse transcriptase polymerase chain reaction
SACE	Serum angiotensin converting enzyme
SD	Standard deviation
SJEH	St John Eye Hospital
SLE	Systemic lupus erythematosus
SOC	Standard-of-care
SUN	Standardization of uveitis nomenclature
TB	Tuberculosis
TB uveitis	Tubercular uveitis
TBU	Tubercular uveitis
TNF-α	Tumour necrosis factor-alpha
TPHA	Treponema pallidum haemagglutination assay
TST	Tuberculin skin test
TTP	Thymine triphosphate
U & E	Urea and electrolytes
UK	United Kingdom
VA	Visual acuity
VKH	Vogt-Koyanagi-Harada
VZV	Varicella zoster virus
WHO	World Health Organization

PREFACE

This thesis is presented to the reader in the University of the Witwatersrand's recommended "divided block" format. In this format, the thesis consists of two parts: the first part includes the Introduction and Methods chapters (Chapters 1 and 2) that are written in the traditional thesis format, and second part written in research publication format in which the Introduction, Methods, Results and Discussion of the study's objectives are presented as individual chapters (Chapters 3, 4 and 5). The main findings of my research are then discussed in the Integrated Discussion and Conclusion chapter (Chapter 6).

This thesis deals with the epidemiology and clinical predictors of tubercular uveitis (TBU) (Chapter 4) in a low-income community setting in Johannesburg, South Africa where the burden of TB and HIV is high. Additionally, the clinical outcome of cases with TBU on anti-tubercular treatment (ATT) was evaluated (Chapter 5). Furthermore, we undertook a systematic review and meta-analysis of TBU prevalence and treatment outcome studies, including studies from sub-Saharan Africa (Chapter 3).

In the Introduction chapter (Chapter 1), the epidemiology, pathogenesis, clinical predictors and treatment of TBU, and challenges with immunological and microbiological or molecular methods in diagnosing TBU, are described.

In Chapter 2, Materials and Methods are described. To address the main objectives, a study was undertaken to determine the prevalence of TBU in adults presenting with uveitis and clinical features predictive of TBU, and to report on the tests (tuberculin skin test (TST), QuantiFERON-TB Gold assay (QFT-G) and TB-PCR assay) used to make the diagnosis of TBU. Furthermore, cases were followed- up to determine the treatment outcomes of TBU when managed with ATT and corticosteroids. Furthermore, to provide context to our study, we conducted a systematic review and meta-analysis of studies on TBU reported up until 30 June 2020.

In Chapters 3, 4 and 5, the introduction, methods, results and discussion of my work in research publication format is presented; the portable document format (pdf) of the published manuscripts in peer-reviewed journals are attached at the end of the thesis (Appendixes 1, 2 and 3). In Chapter 3, the global prevalence and clinical outcome of TBU cases is described. This is a systematic review and meta-analysis. In chapter 4, the prevalence of TBU in uveitis cases

after exclusion of other causes; the clinical predictors of TBU; and the positivity of the TST, QFT-G and TB-PCR is reported. In Chapter 5, the clinical outcome of TBU on ATT is reported. Cases were followed-up for 15 months, and clinical outcome was measured in relation to resolution of inflammation in TBU cases.

The thesis concludes with a summation of the main findings of my research in Chapter 6.

STUDENT CONTRIBUTIONS

Protocol and ethics: The first draft of the study protocols was prepared by HDA. He was responsible for obtaining ethical approval.

Recruitment and follow-up: HDA was responsible for enrolment and consenting of all patients. All TBU and non-TBU cases were treated, and followed-up by HDA.

Laboratory component: Blood sample for QuantiFERON-TB Gold test and ocular fluid sample for microbiological and molecular tests were taken by HDA. The tuberculin skin test was conducted and measured 48 hrs later by HDA. The QuantiFERON-TB Gold test was undertaken by a laboratory technician at Lancet Laboratories.

The microbiological and molecular tests were conducted by Lavania Joseph and overseen by Dr Shaheed Omar at The National TB Reference Laboratory. The TB-PCR assay was developed and validated in-house using published primers targeting the IS6110 and MPB64 genes unique to the Mycobacterium complex. The GeneXpert MTB/RIF (Cepheid, Sunnyvale, CA) assay was performed using the commercial kit / platform.
(Additionally, the Seeplex Meningitis ACE-V1 (Viral) Detection assay (Seegene, Inc., Seoul, South Korea) was performed to detect several viruses, although it was not part of the TBU study)
HDA was familiar with the laboratory techniques.

Statistical analysis: The statistical analyses were performed by HDA and Dr Naseer Ally. The meta-analyses of proportions, multiple imputations, two-level multilevel mixed effects model and generalized estimating equations were performed by Dr Naseer Ally.

CHAPTER 1 INTRODUCTION

Mycobacterium tuberculosis (*Mtb*) is an obligate aerobic slow growing bacterium which successfully grows in oxygen-rich conditions but can survive in oxygen-deprived environments (Katalinic-Jankovic, Furci and Cirillo, 2012). It causes tuberculosis (TB) which is transmitted from one individual to another through aerosol droplets of pulmonary secretions. The micro-organism causes a chronic and indolent systemic disease which can affect any organ in the body, primarily the lungs but also the eyes, meninges, pleura, lymph nodes, abdomen, genitourinary tract, skin, joint and bones (Tabbara, 2007). Tuberculosis of the eye commonly presents independent of pulmonary TB, and frequently (60-93%) presents as tubercular uveitis (TBU) (Donahue, 1967; Biswas and Badrinath, 1995).

Tuberculosis involving the eye is termed ocular TB which is divided into TBU (inflammation of the uveal tract) and tubercular scleritis (inflammation of the sclera) (Agrawal *et al.*, 2019). The most common manifestation of ocular TB is TBU (Donahue, 1967; Shakarchi, 2015b). Tubercular uveitis is diagnosed as confirmed (definite) or presumed (possible or probable) TBU (Gupta *et al.*, 2015). The diagnosis of TBU is 'confirmed' if there is direct evidence of *Mtb* bacilli in ocular fluid samples (aqueous or vitreous humour) and 'presumed' if there is no direct evidence.

Uveitis is defined as intraocular inflammation of the uveal tract, which includes the iris, ciliary body, and choroid of the eye (Grillo, Levinson and Gordon, 2011). Any part of the uveal tract can be involved, and often the inflammation involves adjacent structures such as the cornea, sclera, retina and optic nerve. Inflammation of the uveal tract results in leakage of inflammatory cells in the aqueous humour (located in the anterior part of the eye) and / or vitreous humour (located in the posterior part of the eye) depending on which uveal structure/s are involved. This inflammatory activity is the hallmark of uveitis. Anatomically, uveitis can be classified as anterior (iritis or iridocyclitis), intermediate (pars planitis or posterior cyclitis), posterior (choroiditis, chorioretinitis, retinochoroiditis, retinal vasculitis) and panuveitis (inflammation involving both the anterior and posterior parts of the eye) (Jabs *et al.*, 2005).

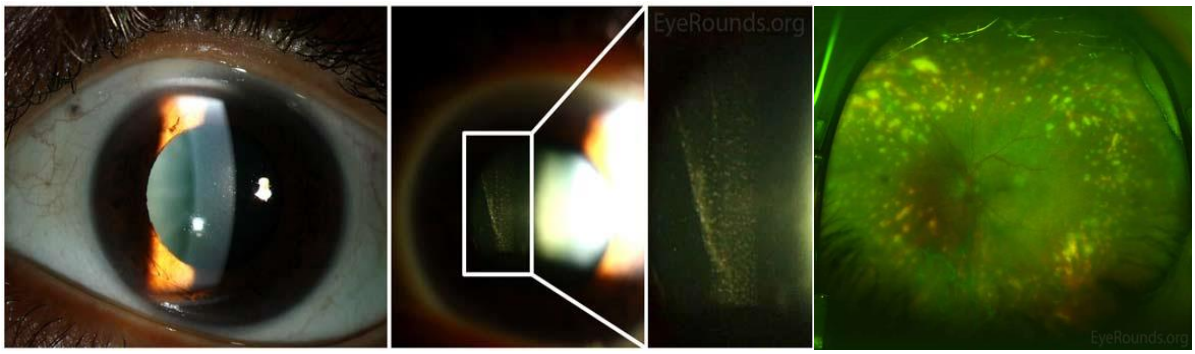


Figure 1.1 Anatomical classification of uveitis (courtesy EyeRounds.org, University of Iowa)

Footnote: Extreme left photograph showing inflammatory cells in anterior chamber of the eye = anterior uveitis
Footnote: Middle two photographs showing inflammatory cells in vitreous humour = intermediate uveitis
Footnote: Extreme right fundus photograph showing multiple inflammatory lesions involving the choroid / retina = posterior uveitis
Footnote: Involvement of all the above 3 structures of the eye = panuveitis

There are multiple causes of uveitis which can be broadly categorized into infectious or non-infectious. Common non-infectious causes are HLA-B27-associated uveitis, sarcoidosis, Vogt-Koyanagi-Harada (VKH) disease, Behcet's disease, Fuchs heterochromic uveitis (FHI), ankylosing spondylitis and juvenile idiopathic arthritis (JIA) (Wakabayashi *et al.*, 2003; Jones, 2015; Gao *et al.*, 2017; Biswas, Kharel and Multani, 2018; Yalçındağ *et al.*, 2018). Common infectious causes include tuberculosis (TB), syphilis, Herpes Simplex Virus (HSV Type 1 and 2), Varicella Zoster Virus (VZV), Cytomegalovirus (CMV) and Toxoplama gondii (Jones, 2015; Gao *et al.*, 2017; Gonzalez Fernandez *et al.*, 2017; Sukavatcharin *et al.*, 2017; Zagora *et al.*, 2017; Chen *et al.*, 2018; Biswas, Kharel and Multani, 2018).

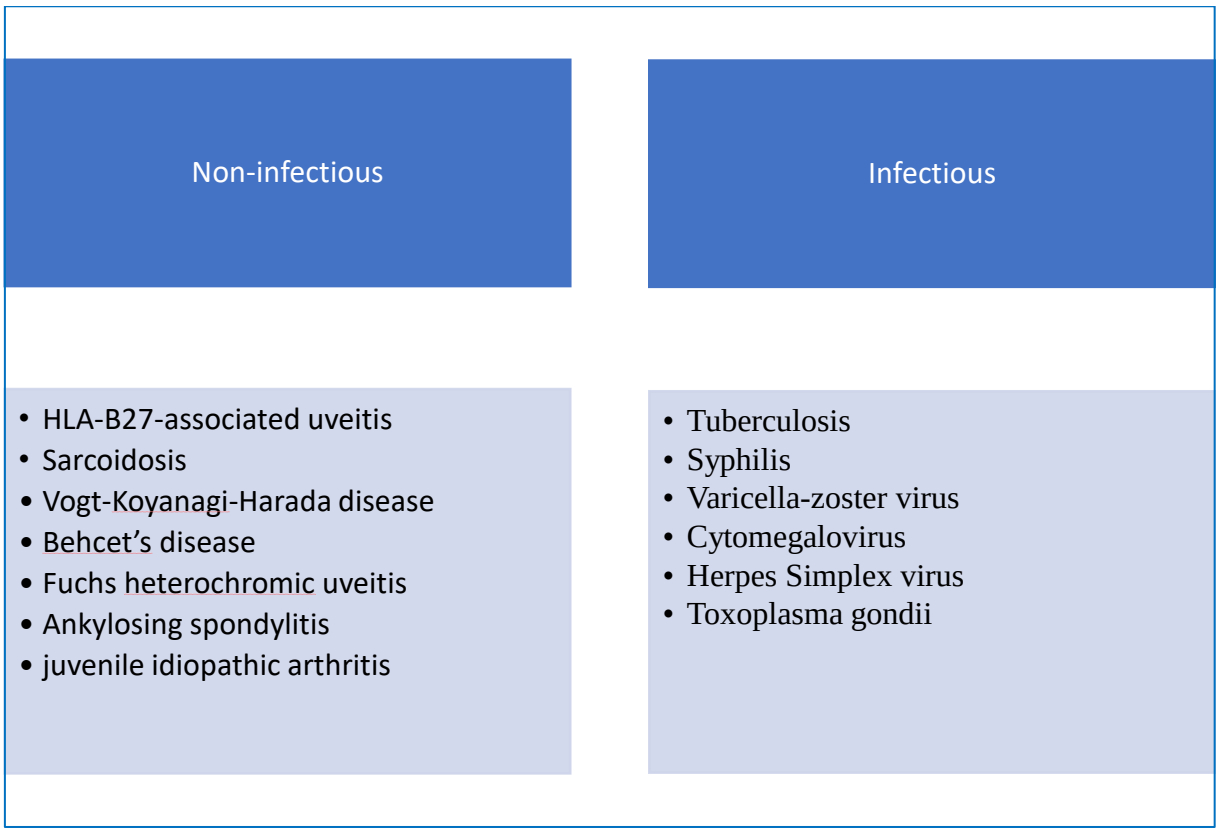


Figure 1.2 Common non-infectious and infectious aetiologies of uveitis

1.1 Epidemiology

Tuberculosis is a global health problem with significant morbidity and mortality. It is the leading cause of death from a single infectious agent (*Global tuberculosis report, 2020*). In 2019, the estimated incidence of TB worldwide was 10.0 million with most of the cases from South-East Asia (44%), Africa (25%) and the Western Pacific (18%) (*Global tuberculosis report, 2020*); South Africa had the eighth highest number of incident cases (3.6%) (*Global tuberculosis report, 2020*). The highest burden of TB was among adult men (56% of all cases) followed by adult women (32%) and children (12%). The male to female ratio for all ages ranged from 1.3 in the Eastern Mediterranean region to 2.1 in the European and Western Pacific regions.

Globally, approximately 8.2% of the incident cases were persons living with the Human Immunodeficiency Virus (HIV); the highest proportion being in the African region (*Global tuberculosis report, 2020*). The risk of developing TB in persons living with HIV was 18% higher than the normal population. In 2019 an estimated 1.2 million deaths occurred from TB among HIV-negative individuals and 208 000 deaths in HIV-positive individuals (*Global tuberculosis report, 2020*).

Of the 7.0 million estimated incident cases of tuberculosis (TB) notified in 2018, 15% were extrapulmonary tuberculosis (EPTB) (*WHO | Global tuberculosis report, 2019*). Persons who

are female were at higher risk (odds ratio ranging from 1.32 to 1.52) of EPTB, and this sex difference has been partly explained by hormonal factors (Qian *et al.*, 2018; Khan *et al.*, 2019). Although the association between HIV and pulmonary TB is well established, the association between HIV and EPTB is modest (odds ratio 1.3) (Naing *et al.*, 2013; Shivakoti *et al.*, 2017). A study in France reported risk factors associated with EPTB varied according to the ancestry of birth (Cailhol, Decludt and Didier, 2005). Extrapulmonary tuberculosis was associated with HIV infection (OR=2.48; 99% CI [1.84-3.34]) in persons of European ancestry; female gender in those of Asian ancestry (OR=1.82; 99% CI [1.31-2.52] and North African ancestry (OR=5.99; 99% CI [3.34-10.7] in women aged 40-59 years) persons; and age (OR=1.63; 99% CI [1.14-2.32] in age range 40-59 years) in sub-Saharan ancestry. Genetic variations of the natural resistance-associated macrophage protein 1 (NRAMP1) was cited as the reason for the different ethnic susceptibility to EPTB. The list of EPTB sites in this study was not completely exhaustive and did not include TB involving the eye and its adnexa (orbits, eyelids, lacrimal system, extraocular muscles, and optic nerve).

The prevalence of TB involving the eye and its adnexa in individuals with pulmonary TB is between 1.4% to 6.8% (Donahue, 1967; Biswas and Badrinath, 1995; Lara and Ocampo Jr., 2013). The reported prevalence of TBU among individuals with uveitis in hospital-based studies varies from 0.18% to 48% (Kotake *et al.*, 1996; La Distia Nora *et al.*, 2018). There are 30 high-burden countries (HBCs) for TB (*Global tuberculosis report, 2020*) and the prevalence of TBU in these countries range from 0.5% to 48% (Biswas *et al*, 1996; La Distia Nora *et al.*, 2018). In non-HBCs for TB, the prevalence range from 0.18% to 44% (Kotake *et al.*, 1996; Gineys *et al.*, 2011). The prevalence of TBU among uveitis cases in South African hospital-based studies range from 8% to 33% (Schaftenaar *et al.*, 2016; Rautenbach *et al.*, 2019; Smit, Esterhuizen and Meyer, 2018). The prevalence of TBU among uveitis cases in two population-based studies was low (0.4%-0.7%) (Acharya *et al.*, 2013; Yalçındağ *et al.*, 2018). The above reported prevalence are for presumed TBU among uveitis cases. There are fewer studies reporting on the prevalence of confirmed TBU (*Mtb* PCR-positive cases); the prevalence range from 37.7% to 70.2% among cases with presumed TBU (Gupta *et al.*, 1998; Arora *et al.*, 1999; Balne *et al.*, 2014; Sudheer *et al.*, 2018; Agarwal *et al.*, 2019).

The lack of a gold standard for the diagnosis of TBU and the lack of standardization in the diagnostic criteria of TBU have contributed to the large variation in the above reported prevalence of TBU in uveitis cases (Gupta, Gupta and Rao, 2007).

1.2 Pathogenesis

Understanding the pathogenesis of TBU is challenging. The original explanation that TBU results from haematogenous spread and direct invasion of local ocular tissues by *Mycobacterium tuberculosis* (*Mtb*) is over-simplistic. The lack of microbiological or molecular evidence of *Mtb* in ocular samples suggests that an immune reaction to *Mtb* antigens or non-viable *Mtb* bacilli in the eye may play a role (Wroblewski *et al.*, 2011; Forrester *et al.*, 2013; Basu, Elkington and Rao, 2020). Another possible explanation is that TBU is an autoimmune reaction whereby distal T-cell priming occurs due to a cross-reaction between *Mtb* and retinal antigens (Garip *et al.*, 2009; Basu, Elkington and Rao, 2020).

1.2.1 The *Mycobacterium tuberculosis* cell wall

Although classified as a Gram-positive micro-organism, the *Mtb* cell wall shares features with that of Gram-negative cells (Alderwick *et al.*, 2015). The cell wall of *Mtb* consists mainly (60%) of complex lipids with long chain fatty acids named mycolic acids (Figure 1.3). These long chain fatty acids which consists of an alkyl side chain and a hydroxyl group at the alpha and beta positions respectively are covalently bonded mainly to the peptidoglycan-arabinogalactan complex of the cell wall (Alderwick *et al.*, 2015). In addition, mycolic acids lipids such as trehalose monomycolate, trehalose monomycolate and glucose monomycolate are constituents of the outer cell envelope. Essential for viability and virulence, these long chain fatty acids make the cell wall impermeable and resistant to acidic and alkaline compounds in the intracellular and extracellular environment and resistant to antimicrobial agents. *Mycobacteria tuberculosis* grows better in oxygen-rich environments, such as the lung but can survive in oxygen-poor conditions. It replicates very slowly (every 20-22 hours) and can persist in a latent state for a long period before clinically manifesting as TB.

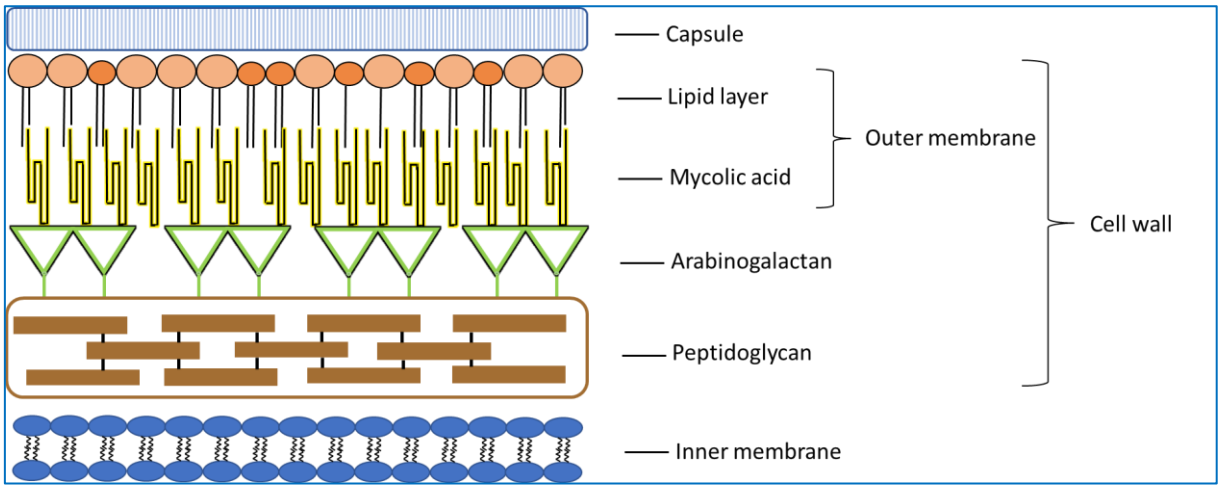


Figure 1.3 Cell wall of *Mycobacterium tuberculosis* bacillus (Courtesy Dr Lieschen Branders, University of the Witwatersrand)

Mycobacterium tuberculosis mainly targets host macrophages which are mediators of both the innate and adaptive immune response.

1.2.2 Innate immunity

After being inhaled, *Mtb* passes through the airways of the lungs and reaches the alveolar spaces where it interacts with dendritic cells, alveolar macrophages, and pulmonary epithelial cells (Sia and Rengarajan, 2019).

Interaction with uptake receptors (complement receptors, mannose receptors and scavenger receptors) and recognition receptors on the macrophages result in phagocytosis of the bacillus and initiation of innate immunity, respectively (Figure 1.4) (Sia and Rengarajan, 2019). Uptake of *Mtb* by macrophages leads to sequestration and eradication of the bacillus via phagolysosomal fusion and acidification (Sia and Rengarajan, 2019). The recognition receptors on macrophages recognise the different *Mtb* components, initiating innate immunity (Sia and Rengarajan, 2019). Stimulation of these recognition receptors induces the expression of cytokines. These cytokines recruit circulating blood monocytes and neutrophils to the site of infection and stimulate T-lymphocytes to produce interferon-gamma (IFN-γ). In the lungs the monocytes differentiate into macrophages, which are then activated by IFN-γ. Neutrophils, via the secretion of antimicrobial molecules and inflammatory mediators, defend against *Mtb* infection (Sia and Rengarajan, 2019). Although recognition of the *Mtb* bacillus results in its destruction, via the initiation of innate immunity, the bacillus has developed strategies to survive in macrophages and neutrophils.

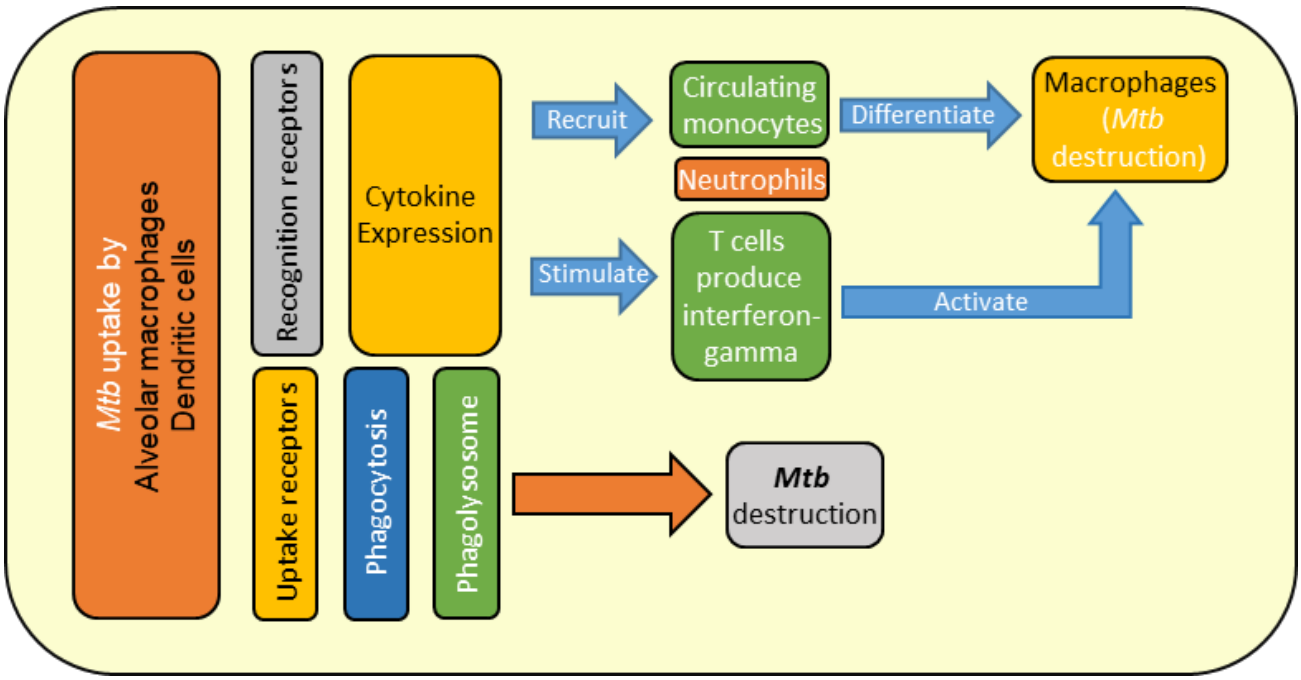


Figure 1.4 Innate immune response to inhaled *Mycobacterium tuberculosis* (*Mtb*)

Interaction of *Mtb* with dendritic cells results in the uptake and presentation of the bacillus to T-lymphocytes in the regional lymph nodes (Sia, Georgieva and Rengarajan, 2015). Thus, these cells are an important mediator between the innate and adaptive immune response. There is a delay in onset of the adaptive immune response to the *Mtb* infection. The delay may be responsible for sufficient *Mtb* bacilli to avoid complete elimination and establishing latent TB infection (LTBI) (Goldberg, Saini and Porcelli, 2014).

1.2.3 Adaptive immunity

Dendritic cells, after migrating to regional lymph nodes, present live mycobacteria to naïve T lymphocytes, priming them (Sia, Georgieva and Rengarajan, 2015). The adaptive immune response mediated by T lymphocytes is critical for control of *Mtb* (Jasenosky *et al.*, 2015). The T-lymphocytes release interferon-gamma (IFN-γ). Interferon-gamma stimulates macrophages to release tumour necrosis factor-alpha (TNF-α), as well as playing a role in intracellular mycobacterial killing. Tumour necrosis factor alpha is important in driving the inflammation and formation of granulomas that wall-off the organism which restricts dissemination; deficiency in TNF-α may lead to disseminated TB (Jasenosky *et al.*, 2015).

The delay in the initiation of the adaptive immune response may result in free *Mtb* or *Mtb* in dendritic cells disseminating to different parts of the body, including the eyes (Goldberg, Saini

and Porcelli, 2014). This may lead to primary active TB or latent TB at these sites. The *Mtb* bacilli in latent TB are dormant and may reactivate at a later stage.

1.2.4 Active TB: Primary infection or reactivation of dormant TB bacilli

Whether most cases of active TB occur due to primary infection or secondary to reactivation of dormant TB bacilli is unclear and could depend on the immune status and the site of active TB (pulmonary or extrapulmonary tuberculosis) (Musellim *et al.*, 2005; Kumar, 2016).
It has been suggested that most active pulmonary TB cases occur within two years of infection, especially in high TB-burden countries where a large proportion of these cases results from progression of primary infection following recent transmission (Behr, Edelstein and Ramakrishnan, 2018). This is supported by reports that in immunocompromised individuals (e.g. HIV-positive individuals), active TB occurs as a result of progression of primary disease, especially in extra-pulmonary sites (Kumar, 2016); high TB-burden countries generally have a high prevalence of HIV. In immunocompetent individuals, active TB is due to reactivation which occurs when the immune system weakens (Kumar, 2016); this may occur decades after the initial exposure.

Evidence suggests that active extrapulmonary tuberculosis in immunocompetent individuals occurs consequent to reactivation of *Mtb* bacilli previously lodged in the extrapulmonary sites from prior lung infection (Wallgren, 1948; Musellim *et al.*, 2005; Qian *et al.*, 2018). A study comparing the time to onset of pulmonary TB versus EPTB following TB contact showed that the likelihood of EPTB was lower (23.7% versus 72.6%) within 5 years of contact (Musellim *et al.*, 2005).

1.2.5 Pathogenesis of tubercular uveitis

Irrespective of the pathogenesis of extrapulmonary TB, the host immune system can eliminate *Mtb* with persistence of immunoreactivity to mycobacterial antigens. The immunological memory that develops following adaptive immunity to *Mtb* infection is measured by the tuberculin skin test (TST) or interferon-gamma release assay (IGRA), both of which can be used to support the diagnosis of extrapulmonary, including TBU (Jasenosky *et al.*, 2015).

The immune reaction in TBU can be direct or indirect. Despite support for the direct effect of viable *Mtb* in the eye, two observations favour the indirect immune mechanism in the pathogenesis of TBU (Figure 1.5). Firstly, the mismatch in TBU between intraocular inflammation and the low detection of *Mtb* in intraocular fluids supports the indirect immune

mechanism. Notwithstanding the problems in the microbiological/molecular diagnostic tests for the detection of *Mtb* infection, studies have reported low *Mtb*-positivity in aqueous or vitreous fluid samples in TBU cases (Gupta *et al.*, 1998; Arora *et al.*, 1999; Sudheer *et al.*, 2018; Agarwal *et al.*, 2019). This is supported by histopathological tests of enucleated eyes of TBU cases with granulomatous inflammation which demonstrated low numbers of *Mtb* bacilli (Wroblewski *et al.*, 2011). Secondly, resolution of TBU cases does not occur with anti-tubercular therapy (ATT) alone but with concomitant corticosteroid treatment (Kee *et al.*, 2016; Agrawal *et al.*, 2017b). Thus, eradication of the *Mtb* infection with ATT alone is inadequate to treat the inflammation associated with TBU.

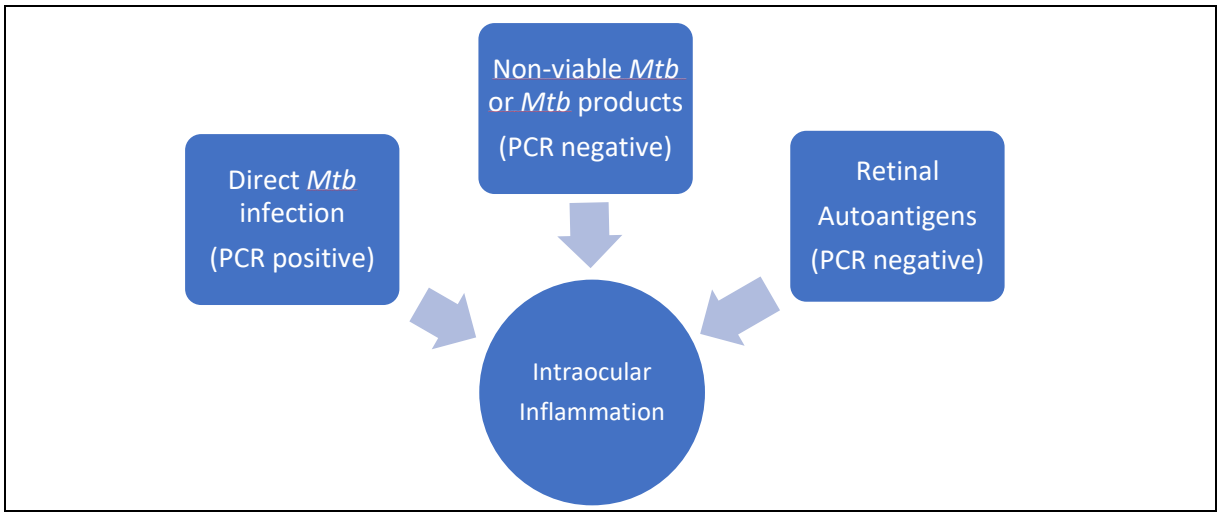


Figure 1.5 Flow diagram of pathogenetic mechanisms involved in tubercular uveitis.

There is evidence to suggest that indirect immune mechanisms are responsible for inflammation in ocular TB (Basu, Elkington and Rao, 2020). These indirect mechanisms, supported by animal and human studies are: i. an immune reaction to non-viable *Mtb* bacilli or its products (proteins or ribonucleic acid) in the eye, and / or ii. an autoimmune reaction whereby distal cell priming of T-lymphocytes cross-react between *Mtb* products (in the eye or elsewhere) and ocular antigens (retinal antigens) (Figure 1.5) (Garip *et al.*, 2009; Basu, Elkington and Rao, 2020). Garip *et al.* reported a case of uveitis secondary to Bacille-Calmette-Gue´rin (BCG) treatment of bladder carcinoma; they concluded that antigen mimicry between tubercular and retinal antigens could be the cause of the uveitis (Garip *et al.*, 2009). Further support for an autoimmune response causing inflammation in TBU is the phenomenon called immune checkpoint inhibition (Basu, Elkington and Rao, 2020). In the treatment of malignancies, this phenomenon causes autoimmune-like adverse events such as

uveitis. In the context of TBU, this means that retinal antigens in the eye that are usually tolerated will elicit an inflammatory response in the absence of inherent physiological restraints on the immune system.

The above different (direct or indirect) immune mechanisms of ocular inflammation may contribute to the different clinical phenotypes of TBU (Basu, Elkington and Rao, 2020). Additionally, it has been proposed that breaching of the blood-retinal barrier (BRB; inner = retinal vascular endothelium and outer = retinal pigment epithelium) may contribute to the different clinical phenotypes of TBU (Basu, Elkington and Rao, 2020). No breach in the BRB results in viable or non-viable *Mtb* bacilli or mycobacterial products (protein or nucleic acids) disseminating to the eye causing anterior uveitis, intermediate uveitis and deeply located choroiditis. Alternatively, a breach in the BRB would allow auto reactive T-cells access to antigens in the retina of the eye, resulting in retinal vasculitis or serpiginous-like choroiditis.

Other determinants of the different clinical phenotypes suggested are dose and anatomical location of the *Mtb* inoculum in the eye, and endemicity of TB (Basu, Elkington and Rao, 2020). Ang *et al.* suggested that endemicity of TB may play a role in the different pathogenetic mechanisms and clinical manifestations of TBU (Ang *et al.*, 2012a). They stated that choroiditis, choroidal granulomas or choroidal abscesses, reportedly seen mainly in high endemic regions, may be due to high *Mtb* load which is detected by PCR or culture of ocular fluids, whereas retinal vasculitis and serpiginous-like choroiditis in low endemic areas, may predominantly be due to an immune mediated reaction to *Mtb* antigen or non-viable *Mtb* bacilli which may be detected by TST or IGRA. Support for the above mechanisms determining the clinical phenotypes of TBU comes from Biswas *et al's* study on TB-PCR-positivity; they reported a high PCR-positivity rate (81.8%) in cases with choroidal abscesses or tubercles and a low PCR-positivity rate (41.3%) in cases with serpiginous-like choroiditis (Biswas *et al.*, 2016). However, this is not supported by other studies on PCR-positivity (Gupta *et al.*, 1998; Sudheer *et al.*, 2018; Agarwal *et al.*, 2019).

1.3 Diagnosis

The diagnosis of TBU is difficult. There are neither specific clinical signs, nor microbiological, molecular or immunological tests with high positive predictive value for diagnosing TBU. Consequently, the diagnosis of TBU is often based on a combination of the following diagnostic criteria: (1) suggestive ocular clinical findings; (2) exclusion of other causes of uveitis; (3) positive microbiological (microscopy and culture) or molecular tests (PCR) of ocular fluids; (4)

positive immunological (TST and/or IGRA) tests; (4) chest x-ray or chest CT scan; (5) positive microbiological or molecular tests of pulmonary or other extrapulmonary tissues; and (6) clinical response to ATT (Gupta, Gupta and Rao, 2007; Vasconcelos-Santos, Zierhut and Rao, 2009; Gupta *et al.*, 2015). The challenges and problems with each of the above diagnostic criteria will be discussed below. Clinical response to ATT will be discussed under the heading '1.3.3 Treatment of tubercular uveitis' below.

1.3.1 Ocular clinical features

A wide array of clinical signs in TBU cases have been described, including: (1) anterior uveitis (granulomatous, non-granulomatous, iris nodules, ciliary body tuberculoma), (2) intermediate uveitis (granulomatous, non-granulomatous with organizing exudates in the pars plana/peripheral uvea), (3) posterior uveitis and panuveitis (choroidal tubercle, choroidal tuberculoma (Figure 1.6), subretinal abscess and serpiginous-like choroiditis (Figure 1.7)), (4) retinitis and retinal vasculitis, (5) neuroretinitis and optic neuropathy, (6) endophthalmitis and panophthalmitis (Gupta, Gupta and Rao, 2007).

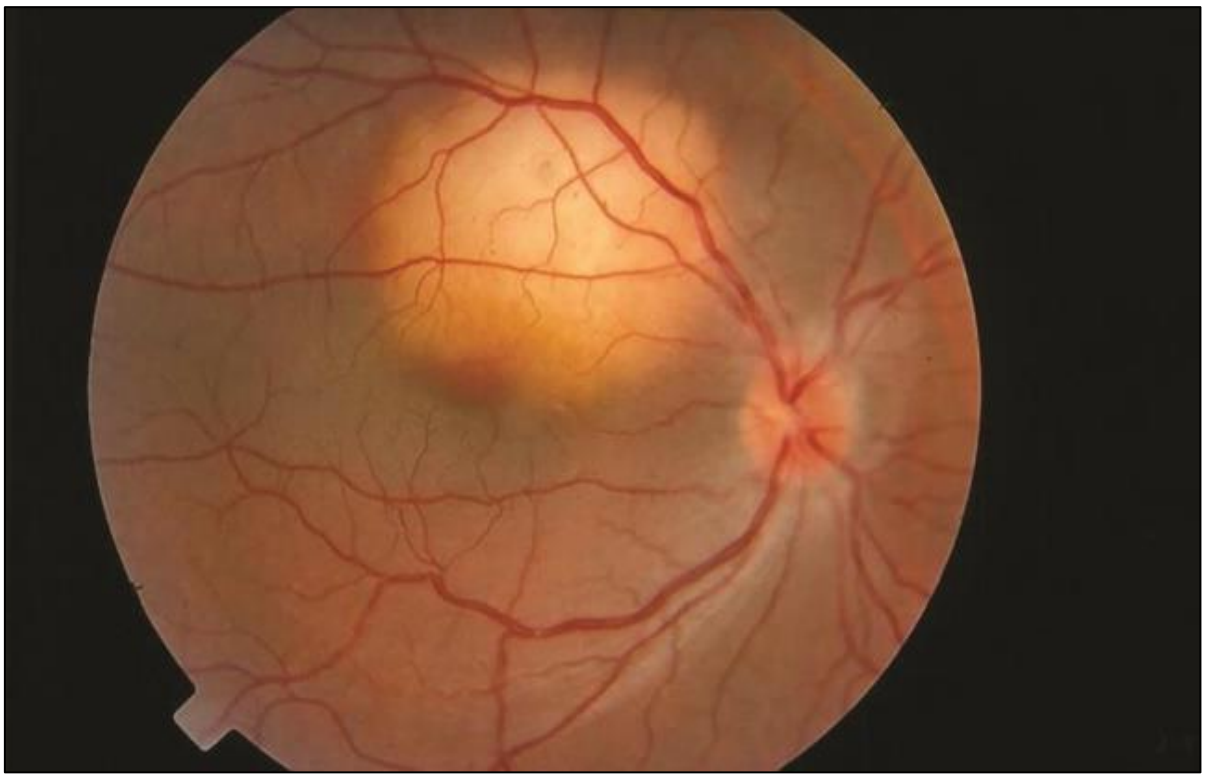


Figure 1.6 Colour fundus photograph of right eye showing large choroidal granuloma (courtesy St John Eye Hospital)

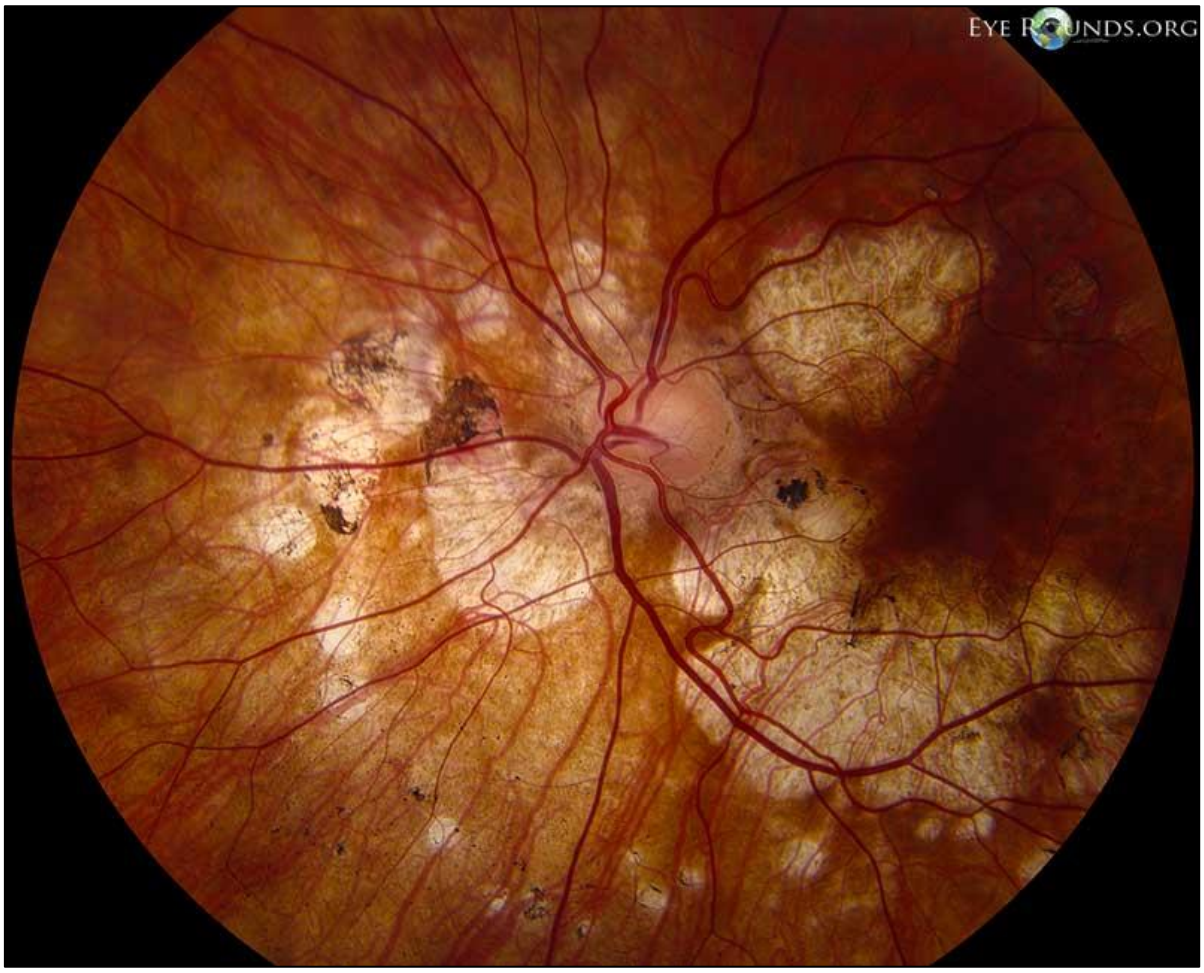


Figure 1.7 Colour fundus photograph of left eye showing serpiginous choroiditis (courtesy EyeRounds.org, University of Iowa)

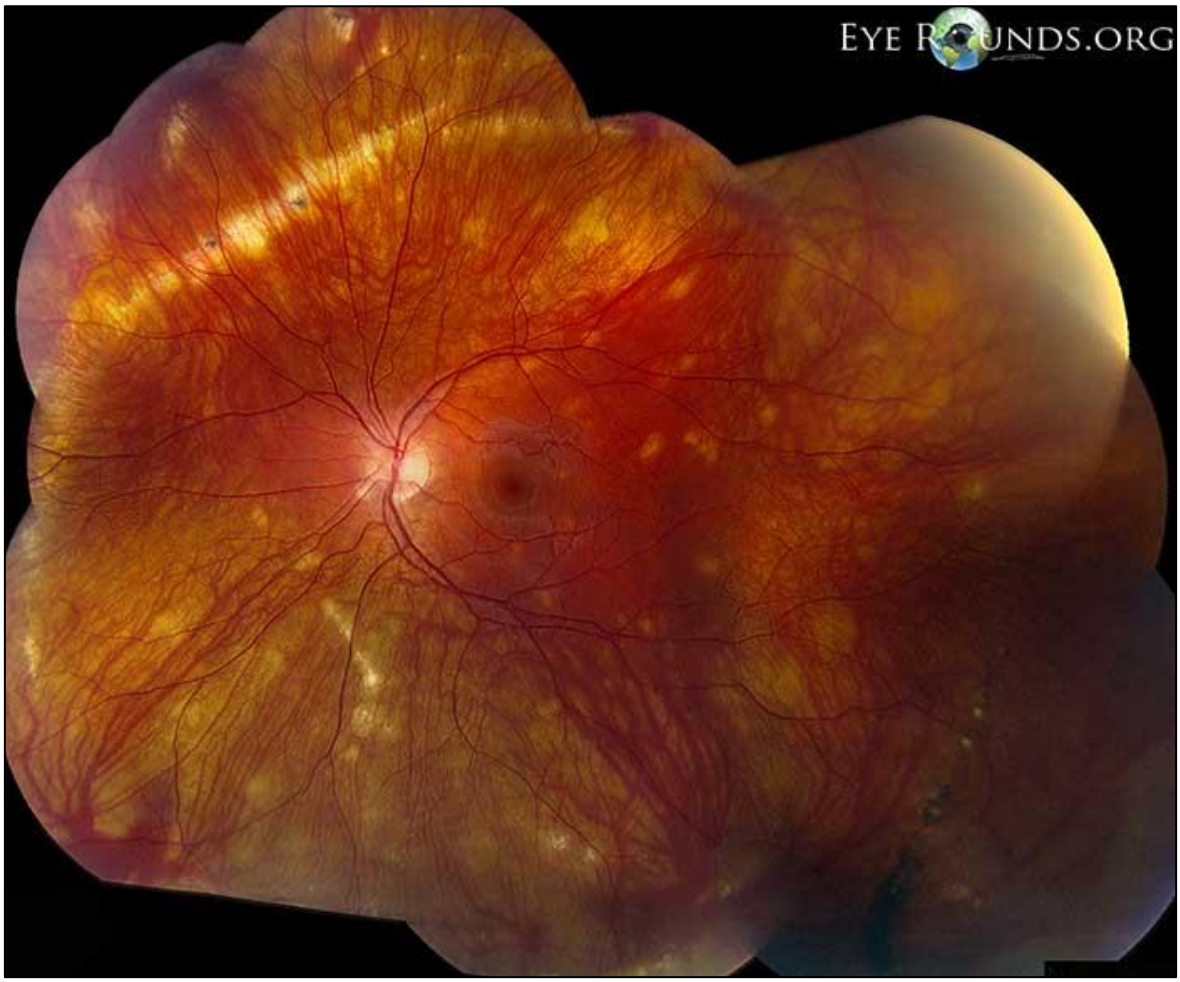


Figure 1.8 Colour fundus photograph of left eye showing multiple choroidal lesions = multifocal choroiditis (courtesy EyeRounds.org, University of Iowa)

Although there are no hallmark ocular clinical signs to diagnose TBU, ocular signs suggestive of TBU have been described (Gupta *et al.*, 2010; Ang *et al.*, 2012a; Gupta *et al.*, 2015; Agrawal *et al.*, 2020b). These include broad-based posterior synechiae, retinal vasculitis with or without choroiditis/choroidal scars, serpiginous-like choroiditis (Figure 1.7) and choroidal granulomas (single or multifocal) (Figure 1.6) (Gupta *et al.*, 2015). Ang *et al.* reported that a single ocular sign was not suggestive of TBU, but rather a combination of ocular signs together with a positive interferon-gamma release assay (IGRA) and tuberculin skin test (TST) (Ang *et al.*, 2012a). Their study, from a country with an intermediate burden of TB disease, showed that together with these tests, a combination of extensive posterior synechiae and anterior scleritis in anterior uveitis, and a combination of low-grade anterior chamber activity, retinal vasculitis and severe vitritis in intermediate, posterior or panuveitis was highly predictive of TBU. They suggested that choroiditis, choroidal granulomas or choroidal abscesses are seen mainly in countries with high burden of TB whereas retinal vasculitis and serpiginous-like choroiditis are seen in countries with low burden of TB. However, Gupta et al. reported that retinal vasculitis

with or without choroiditis and serpiginous-like choroiditis, in addition to broad-based posterior synechiae, are ocular signs more suggestive of TBU in TB-endemic areas (Gupta *et al.*, 2010). The Collaborative Ocular Tuberculosis Study (COTS) group identified serpiginous-like choroiditis and choroidal granulomas to be strongly associated with TB in countries with high and low burden of TB and warranting ATT; non-serpiginous multifocal and unifocal choroiditis were 'considered not suggestive of TB infection' (Agrawal *et al.*, 2020b).

In terms of the anatomical classification, the predominant TBU type in several studies is panuveitis (Al-Mezaine, Kangave and Abu El-Asrar, 2010; Gineys *et al.*, 2011; Sanghvi *et al.*, 2011). In the COTS study the most common anatomic presentation was posterior uveitis followed by panuveitis (Agrawal *et al.*, 2017a). Severe visual impairment is associated with posterior or panuveitis (Basu *et al.*, 2014; Gunasekeran *et al.*, 2018).

Tubercular uveitis can result in ocular morbidity such as visual impairment and blindness (Basu *et al.*, 2014; Gunasekeran *et al.*, 2018). Visual impairment is usually due to macular oedema, glaucoma, vitreous haemorrhage, cataract, and macular scarring (Basu *et al.*, 2014; Gunasekeran *et al.*, 2018). Adverse visual sequelae following TBU are associated with delay in diagnosis, chronic disease, and posterior uveitis with choroiditis (Gunasekeran *et al.*, 2018; Basu *et al.*, 2014; Patel *et al.*, 2013).

1.3.2 Diagnostic tests

Microbiological / Molecular

The diagnosis of TBU by the different diagnostic tests is challenging. The definitive method for establishing a diagnosis is by detecting *Mtb* through microscopy (acid-fast bacillus [AFB] smear) and culture of ocular fluid (aqueous or vitreous) (Gupta, Gupta and Rao, 2007; Yeh *et al.*, 2012). However, these diagnostic methods are not ideal because they have low positive yield due to the pauci-bacillary nature of TBU (Gupta, Gupta and Rao, 2007; Wroblewski *et al.*, 2011). For *Mtb* to be detected on a smear, at least 10^6 bacilli/ml of fluid are needed (Gupta, Gupta and Rao, 2007). Culture is time-consuming and requires a large sample, and often does not give a positive result because of the low yield of *Mtb* from ocular fluids (Gupta, Gupta and Rao, 2007). Molecular techniques are currently the diagnostic tool of choice for the rapid detection of *Mtb*, albeit also not being ideal for the diagnosis of TBU.

The most widely used molecular tool for the diagnosis of infectious diseases, including TB, are the nucleic acid amplification techniques which are polymerase chain reaction (PCR) and reverse transcriptase PCR (RT-PCR) (Ieven and Goossens, 1997). The PCR and RT-PCR detects micro-organisms whose primary genetic material is deoxyribonucleic acid (DNA) and

ribonucleic acid (RNA), respectively. Polymerase chain reaction amplifies minute quantities of DNA or RNA to large number of copies (≥107 copies) for the detection of bacteria and viruses in a short period. It involves 3 processes: extraction of DNA or RNA from clinical samples, amplification of DNA or RNA targets and detection of amplified targets (Ieven and Goossens, 1997). The test uses short single-stranded segments of DNA called primers, the sequences of which are complimentary to sequences of the intended DNA target, for example that of *Mtb*. The primers, together with DNA polymerase, deoxynucleotides (ATP, TTP, GTP, CTP) and necessary reagents are added to a solution that contains the *Mtb* DNA (and host DNA) which is derived from the ocular fluid sample. The reaction mix is heated to separate the DNA into its two strands (denaturation) and then cooled to allow the primers to attach to complimentary regions of the target *Mtb* DNA (annealing). The reaction mix is heated again to promote the addition of nucleotides to the primer ends, thus building a 'new' of DNA (extension by DNA polymerase). The PCR mix undergoes 25 to 40 cycles of heating and cooling to amplify the target *Mtb* DNA. Thus, discrete fragments of deoxyribonucleic acid (DNA) fragments of *Mtb* are amplified and can be detected in samples where the target sequence is present in minute quantities.

For the diagnosis of pulmonary and extrapulmonary TB, commercial tests such as the GeneXpert MTB/RIF (Xpert) (Cepheid, Sunnyvale, CA) assay are used (Boehme *et al.*, 2010; Hillemann *et al.*, 2011; Vadwai *et al.*, 2011); it is a real-time PCR assay to detect the MTB-specific sequence of the rpoB gene. It detects *Mtb* bacilli and screens for rifampicin resistance. The advantages of this assay are: (1) results could be available in less than two hours, (2) not prone to cross-contamination, (3) can be performed by technicians with minimal training (Boehme *et al.*, 2010; Vadwai *et al.*, 2011). The disadvantage of the assay is that it has low sensitivity in extrapulmonary, paucibacillary TB samples, especially cerebrospinal fluid (CSF) and pleural fluid samples (Vadwai *et al.*, 2011; Penz *et al.*, 2015). Over the years, the Xpert MTB/RIF assay has evolved through four versions, with improved sensitivities with each version.

In the diagnosis of extrapulmonary TB, the older versions of the GeneXpert MTB/RIF assay, the Xpert, had lower sensitivities. The combined sensitivity and specificity in extrapulmonary TB (different tissue and fluid samples which did not include the eye) was shown to be over 75% and 95%, respectively (Hillemann *et al.*, 2011; Vadwai *et al.*, 2011). In one study, the CSF had a very low sensitivity (29%) (Vadwai *et al.*, 2011). In another study, the sensitivity of the Xpert varied by specimen types due to the different bacillary loads of the different specimens; it was

low in pleural fluid specimens (37%) but high (87%) in fine-needle aspiration (FNA) of lymph nodes (Penz *et al.*, 2015).

The latest version of the GeneXpert MTB/RIF, the Xpert Ultra, has been shown to display higher sensitivity albeit no improvement in specificity and rifampicin resistance detection (Opota *et al.*, 2019). It has an improved limit of detection (LOD) for *Mtb* from sputum (~ 15.6 colony forming units [cfu] / ml) compared to the Xpert (~112.6 cfu / ml); the Xpert Ultra targets multicopy sequences, namely IS6110 (~16 copies/cell) and IS1810 (~5 copies/cell) while Xpert targeted the single copy gene rpoB (Chakravorty *et al.*, 2017). In smear-negative, culture positive respiratory specimens, the sensitivity of the Xpert Ultra assay was higher (63% - 78.9%) than the Xpert assay (46% - 66.1%) (Chakravorty *et al.*, 2017; Dorman *et al.*, 2018), including in HIV-positive cases (90% versus 77%) (Dorman *et al.*, 2018). The Xpert Ultra, compared to the Xpert, has increased sensitivity in diagnosing paucibacillary TB (Wang *et al.*, 2019). The overall sensitivity of the Xpert Ultra in extrapulmonary TB (EPTB) was higher (83.7%) than the Xpert (67.4%), including CSF (44.19% versus 18.60%) and pleural fluid (43.7% versus 20.4%) (Wang *et al.*, 2019). In another study, the sensitivity of the Xpert Ultra was higher (70%) than the Xpert (43%) in CSF samples of HIV-positive TB meningitis cases (Bahr *et al.*, 2018). This study highlighted the challenges in diagnosing TB meningitis because of the paucibacillary nature of CSF, limited CSF volume (~ 1 ml) being tested, and the high rate of culture-negative TB meningitis. The diagnosis of TBU poses an even bigger challenge because of the paucibacillary nature of ocular fluid and its even smaller volume (~ 0.2 – 0.4 ml) for testing. There are limited studies on the Xpert and none on the Xpert Ultra for the diagnosis of TBU (Bansal *et al.*, 2015; Sharma *et al.*, 2017). In one study, the positive yield of the Xpert on vitreous fluid samples for the diagnosis of TBU was 22.3% (Sharma *et al.*, 2017). In another study, the positive yield of *Mtb* from vitreous fluid samples by the Xpert assay was 36.3% (Bansal *et al.*, 2015).

Many low-income regions with high TB burden cannot afford the Xpert and Xpert Ultra assays due to limited infrastructure and medical resources (Wei *et al.*, 2019). In-house polymerase chain reaction (hPCR) is more affordable, feasible, and sustainable than the Xpert MTB/RIF (Wei *et al.*, 2019). Thus, hPCR is becoming popular in resource-constrained areas. Several regions of the mycobacterial genome, such as IS6110, MPB64 and 16S rDNA, have been used as targets for assays (Sharma *et al.*, 2013; Wei *et al.*, 2019). The IS6110 gene is widely used for pulmonary and extra-pulmonary TB diagnosis. The presence of multiple copies of this gene in the genome of the *Mtb* complex has resulted in increased sensitivity of PCR in detecting this gene. A meta-analysis of studies demonstrated that compared with commercial tests, the

diagnostic accuracy of hPCR assays was variable and inconsistent (Wei *et al.*, 2019). This is largely due to the heterogeneity of the test and the lack of standardization of in-house primers between different laboratories.

In clinically suspected TB cases, a PCR-positivity rate of 4.8% to 70.0% in various smear-negative samples (blood, urine, cerebrospinal fluid (CSF), ascitic fluid, pleural fluid, pericardial fluid, pus, bone marrow, sputum and bronchoalveolar lavage) has been reported (Amin *et al.*, 2011). The advantage of PCR is that it can be performed with a small sample size. However, hPCR assays on ocular fluids for the diagnosis of TBU are rarely performed because: 1) the TB-PCR-positivity is usually low (37.7 – 58.8%), and 2) the results vary due to the lack of standardization of the protocol and technique between different laboratories (Gupta *et al.*, 1998; Arora *et al.*, 1999; Sudheer *et al.*, 2018; Agarwal *et al.*, 2019). Of 962 TBU cases from 25 centres in the COTS-1 multicentre study, only 59 (6.1%) underwent TB-PCR analysis (Agarwal *et al.*, 2019). The PCR-positivity rate of the 59 cases was 55.9%. In single centre studies using single-target PCR assays, the TB-PCR-positivity rate is low ranging from 37.7% - 58.8% (Gupta *et al.*, 1998; Arora *et al.*, 1999; Sudheer *et al.*, 2018). In one study, the positivity rate using multi-targeted PCR, where several genes (IS6110, MPB64 and protein b) were simultaneously amplified, was reportedly high (77.8%) (Sharma *et al.*, 2013).

The limitations of microbiological and molecular tests means that supportive investigations, such as the tuberculin skin test and the interferon-gamma release assay, are relied upon for the diagnosis of TBU.

Immunological

1. Tuberculin skin test

Tuberculin skin testing (TST), such as the Mantoux method (Statens Serum Institute, Copenhagen, Denmark), has aided in the diagnosis of TB since the early 1900's. It is rapid and cost-effective. Interpretation of TST is difficult and it must be interpreted considering immunosuppression, timing of previous BCG vaccination and exposure to previous non-tuberculous mycobacteria (NTM) (Farhat *et al.*, 2006; Menzies, Pai and Comstock, 2007). In immunosuppressed individuals, it has a low sensitivity (Menzies, Pai and Comstock, 2007). The TST lacks specificity, especially in high BCG (Bacille-Camille-Guérin) populations within ten years of vaccination and in populations with a high prevalence of NTM (Farhat *et al.*, 2006). Positive tuberculin reactions (≥10 mm) in schoolchildren and young adults more than 10 years after receiving BCG vaccination in infancy was found not to be attributed to the BCG vaccination (Menzies and Vissandjee, 1992; Farhat *et al.*, 2006). Thus, the effect on TST of

BCG received in infancy is similar to non-vaccinated populations, especially ≥ 10 years after vaccination. Non-tuberculous mycobacteria is a clinically important cause of false-positive TST in populations with a high prevalence of NTM sensitisation and a very low prevalence of TB infection (Farhat *et al.*, 2006).

Guidelines for interpreting the TST depend on the individuals risk for TB infection (*Fact Sheets | Testing & Diagnosis | Fact Sheet - Tuberculin Skin Testing | TB | CDC*, 2020). In high-burden regions for TB, an induration greater and equal to 10 mm (≥ 10 mm) is regarded as reactive and suggestive of TB infection. In HIV positive and other high-risk individuals, an induration ≥ 5 mm is reactive and in individuals with no known risk factors it is ≥ 15 mm. However, a reactive TST does not distinguish between latent infection and active TB.

Tuberculin skin testing in the diagnosis of TBU has evolved. In the past, a positive test in uveitis cases merited a trial of isoniazid (INH) for the diagnosis of TBU (Abrams and Schlaegel, 1982, 1983). Subsequently, a positive TST was interpreted together with other clinical signs of TBU for the diagnosis of TBU (Morimura *et al.*, 2002). Recently, the TST has been used together with the interferon-gamma related assay (IGRA) to improve the diagnosis of TBU (Menzies, Pai and Comstock, 2007; Rahman, Irfan and Siddiqui, 2021).

2. Interferon-gamma release assay (IGRA)

The IGRA was introduced in 2001. It measures interferon-gamma released by T lymphocytes stimulated by antigens (ESAT-6 [early secreted antigenic target 6] and CFP-10 [culture filtrate protein 10]) specific to *Mtb* (Rahman, Irfan and Siddiqui, 2021). These antigens are encoded by genes in the RD1 (region of difference 1) locus of the *Mtb* genome. These genes are absent from the BCG strain *Mycobacteria bovis* and non-tuberculous mycobacteria such as *Mycobacteria avium* (Menzies, Pai and Comstock, 2007). Consequently, the IGRA is more specific than TST and is not influenced by previous BCG vaccination and non-tuberculous mycobacterial infections. Other advantages of the IGRA over the TST are that (1) the test requires only 1 visit, (2) adverse events are reduced and (3) there is no booster effect (Menzies, Pai and Comstock, 2007). The disadvantages of the IGRA over the TST are (1) that it requires drawing of blood and careful handling of the drawn blood, (2) higher material costs, and (3) the need for an equipped laboratory (Menzies, Pai and Comstock, 2007).

There are 2 commercial types of IGRAs available: QuantiFERON-TB (QFT) assay (Cellestis/Qiagen, Carnegie, Australia) and the T-SPOT.TB assay (Oxford Immunotec, Oxford, UK). The first version of the QFT assay was approved by the FDA in 2001, and since 2017 the fourth version is in use (Rahman, Irfan and Siddiqui, 2021). The sensitivity of the older version

of the QFT (QuantiFERON-TB Gold In-Tube assay [QFT-G]) assay was 69% - 89% for active TB and 58% - 84% for latent TB (Rahman, Irfan and Siddiqui, 2021). The sensitivity for active (94%) and latent (91%) TB has improved with the newer QuantiFERON-TB Gold Plus assay (Rahman, Irfan and Siddiqui, 2021). The specificity of this new version of the QFT assay is also high for active (96%) and latent (95%) TB (Rahman, Irfan and Siddiqui, 2021). The T-SPOT.TB assay has been approved for use since 2004. In a meta-analysis, the pooled estimates of sensitivity for the TSPOT.TB assay was reportedly higher (88%) than the QFT assay (76%) and the TST (70%) (Menzies, Pai and Comstock, 2007). In HIV-positive individuals with severe immunodeficiency, the sensitivity of the TSPOT.TB assay is higher than the QFT assay and TST (Reviono *et al.*, 2019; Rahman, Irfan and Siddiqui, 2021).

Using Bayesian analysis, Ang et al. reported IGRAs having a sensitivity of 64% - 67% in diagnosing TBU (Ang *et al.*, 2014b). The combination of the QFT assay and TST may be more useful than the QFT assay alone in diagnosing TBU (Babu *et al.*, 2009b; Ang, Htoon and Chee, 2009). There is a paucity of studies on the TSPOT.TB assay in the diagnosis of TBU, especially in people living with HIV (PLWH). In a head-to-head comparison, the QFT assay (67%) was similar to the TSPOT.TB assay (64%) in diagnosing TBU (Ang *et al.*, 2014b). There are no studies on the usefulness of the latest version of the QFT assay (QuantiFERON-TB Gold Plus assay) in the diagnosis of TBU.

The issues with the microbiological / molecular and immunological diagnostic tests highlighted above indicate that these tests are not singularly helpful in diagnosing TBU. Although a combination of tests might be helpful in diagnosing TBU, clinical response to empiric anti-tubercular (anti-TB) treatment is often warranted to support the diagnosis.

1.3.3 Treatment of tubercular uveitis

In the absence of hallmark ocular clinical features and reliable diagnostic tests, the clinical response to anti-tubercular treatment (ATT) is often taken as supportive evidence of TBU (Gupta, Gupta and Rao, 2007; Gupta *et al.*, 2015). The clinical outcomes, specifically the clinical response to ATT, during treatment and / or after its completion, is usually determined by measuring the improvement or resolution of inflammation in the aqueous humour, vitreous humour and uveal structures. Systemic and / or topical corticosteroids are often used in combination with multi-drug ATT, to control the inflammation and limit the damage to ocular tissues (Kee *et al.*, 2016). In PLWH with TBU, ATT is started before anti-retroviral therapy

(ART) because of the possible paradoxical worsening of inflammation and TB due to immune reconstitution syndrome (IRIS) (Babu *et al.*, 2006).

There are variable clinical responses (24% - 100%) to ATT (Ang *et al.*, 2012b; Manousaridis *et al.*, 2013; Shakarchi, 2015a); this is partly due to the misdiagnosis of TBU, resistance to ATT, variation in ATT regimen (including treatment duration), and the variation in the concomitant corticosteroid use to control inflammation. Good recovery rates on ATT, with / without corticosteroids, have been shown in individuals with presumed TBU (93-100%) (Manousaridis *et al.*, 2013; Shakarchi, 2015a; Chung and Li, 2018) and definite TBU (90%-92%) (Gupta *et al.*, 1998; Balne *et al.*, 2014). A systematic review of treatment outcomes in individuals with presumed TBU reported a recovery rate of 84% on ATT (Kee *et al.*, 2016). However, lower recovery rates (24% to 67%) in presumed TBU cases have been described (Ang *et al.*, 2012b; Ng *et al.*, 2017; Krassas *et al.*, 2018). A multicentre study by the Collaborative Ocular Study (COTS) group reported a recovery rate of 87% (Agrawal *et al.*, 2017a). A 2-year follow-up of TBU cases from this study yielded a lower recovery rate of 77% (Agarwal *et al.*, 2020); the COTS group defined 'cure' as TBU inactivity 2 years after completing ATT. Longitudinal studies assessing clinical outcomes in terms of recurrence of inflammation after inflammation is controlled, are rare (Bansal *et al.*, 2008; Tomkins-Netzer *et al.*, 2018). These studies on presumed TBU cases report reduced recurrence rates in cases treated with ATT and corticosteroid / immunosuppressive treatment (16% - 30%) compared to cases treated with corticosteroids / immunosuppressive (47% - 48%) alone.

The World Health Organization (WHO) guidelines for ATT recommends more than 6 months of treatment for extrapulmonary TB of the central nervous system, bone or joint (World Health Organization and World Health Organization, 2010). They advocate the use of 4 drugs (Rifampicin [R], Isoniazid [H], Pyrazinamide [Z] and Ethambutol [E]) for the first 2-month period followed by 2 drugs (Rifampicin and Isoniazid) for longer than 4 months. There are no treatment duration guidelines for TBU.

The optimal duration of ATT yielding a good treatment response with minimal risk of adverse events has been debated. Alvarez *et al.*, and Vos *et al.* mentioned that treatment for presumed TBU should be stopped in cases responding poorly after 2 – 4 months of ATT (Alvarez, Roth and Hodge, 2009; Vos *et al.*, 2013). However, this may be too early to consider terminating treatment as other studies have reported poor treatment outcomes in cases treated for a shorter duration (Ang *et al.*, 2012b; Agrawal *et al.*, 2015). Cases receiving ATT and concomitant corticosteroids for 3 months had a lower recovery rate (50%) than cases treated for 9 months or longer (77%) (Agrawal *et al.*, 2015). Another study reported an eleven-fold decrease in the

likelihood of recurrence of inflammation in TBU cases treated with ATT for ≥ 9 months compared to cases treated < 9 months (Ang *et al.*, 2012b). A longitudinal study assessing recurrence rates in TBU cases treated with concomitant ATT and corticosteroids for at least 12 months reported a low recurrence rate (16%) (Bansal *et al.*, 2008). Another longitudinal study reported a recurrence rate of 30% in TBU cases treated with a similar regimen for 6 months (Tomkins-Netzer *et al.*, 2018).

The above highlights the issues regarding the diagnosis and treatment of TBU. There are no reliable ocular clinical features and diagnostic tests for its diagnosis. Additionally, there is no consistent and standardized diagnostic criteria; these criteria vary between different institutions and even between patients within the same institution. This has probably resulted in underestimation or overestimation of the prevalence rates of TBU in different regions of the world. In terms of the management of TBU, there is no standardized treatment regimen.

The rationale for my study was to address the gaps in the knowledge of TBU, which were explored through the objectives of my thesis. The following gaps were identified and addressed:

1) The global prevalence of TBU and the pooled prevalence of TBU in high-burden countries, including in sub-Saharan Africa, is not known. Because of this, and to put the study in our setting (see points below) in context of the global prevalence, a systematic review and meta-analysis was undertaken to determine the prevalence of TBU globally; in high-burden versus non-high-burden countries for TB; and regionally, including in sub-Saharan Africa.

2) The prevalence of TBU in our setting / region, where the prevalence of HIV is high, is not known. As part of my PhD thesis, a prospective cohort study was undertaken to determine the prevalence of TBU in our setting / region using standardized criteria, and to determine the ocular clinical features predictive of TBU.

3) The treatment outcome of TBU in our setting / region is also not known. As part of my PhD thesis, patients were followed-up for 15 months to determine the treatment outcomes of TBU on standardized anti-tubercular regimen.

CHAPTER 2 METHODS

All the objectives of the study, including the systematic review and meta-analysis, will be mentioned in this chapter. The methods for the study in our setting at St John Eye Hospital will be described in detail in this chapter. The methods for the systematic review and meta-analysis are described in detail in the manuscript in Chapter 3.

2.1 Study Objectives

2.1.1 Epidemiology and clinical outcomes of tubercular uveitis (TBU) globally through a systematic review and meta-analysis

1. To determine the global prevalence of TBU among individuals presenting with uveitis. Additionally, to determine the pooled prevalence of TBU in individuals presenting with all-cause uveitis in 1) High-burden countries (HBCs) versus non-HBCs for TB, and 2) different geographic regions, including sub-Saharan Africa.
2. To evaluate the clinical outcomes of TBU on anti-tubercular treatment (ATT) globally, and in HBCs versus non-HBCs for TB.

   (Since the methodology of the systematic review and meta-analysis is completely different from my study at St John Eye Hospital, it will not be covered further in this chapter – it is covered in detail in the manuscript in Chapter 3. The methodology covered in the rest of this chapter is that of the study conducted at St John Eye Hospital)

2.1.2 Epidemiology and clinical predictors of tubercular uveitis in a high TB and HIV setting

1. To determine the prevalence / proportion of TBU in a population of uveitis cases (after exclusion of other causes of uveitis) over a five-year period from June 2014 to November 2018.
2. To evaluate the clinical features predictive of TBU.
3. To report on the tests (TST, QFT-G assay and TB-PCR assay) used to diagnose TBU.

2.1.3 Treatment outcomes of tubercular uveitis on anti-tubercular treatment in a high TB and HIV setting

1. To determine the treatment outcomes of TBU cases on ATT together with corticosteroid therapy. Treatment outcomes were measured in terms of time to resolution of inflammation.

2.2 Study Population

2.2.1 Description of the study population in our setting

Saint John Eye Hospital (SJEH) is the Ophthalmology Department of Chris Hani Baragwanath Academic Hospital (CHBAH) situated in Soweto, a peri-urban suburb of Johannesburg in South Africa which has the highest prevalence of human immunodeficiency virus (HIV) infection in the world (*UNAIDS Programme Coordinating Board sees South Africa's AIDS response first-hand*, 2018). It is a public tertiary referral hospital with limited resources serving the low-income population, predominantly black-Africans. Ophthalmic care of individuals without access to private health insurance (80-90%), generally occurs either at government-funded public hospitals (secondary or tertiary) or primary healthcare clinics.

Ophthalmic cases are referred to SJEH from: 1) other departments at CHBAH; 2) primary level clinics in the Johannesburg Metropolitan region (sub-districts D and G) (Appendix 4); and 3) secondary level healthcare hospitals in the Gauteng districts of, i. the Johannesburg Metropolitan region (Lenasia South and Bheki-Mlangeni hospitals), ii. West Rand (Leratong Hospital), iii. Sedibeng (Sebokeng Hospital) and iv. Ekhuruleni (Thelle Mogoerane Hospital) (Appendix 5). Additionally, SJEH receives referrals from Klerksdorp-Tshepong Hospital and Potchefstroom Hospital, which is situated in another province, the North-West Province.

The out-patient department (OPD) at SJEH has a general clinic manned mainly by registrars who assess, investigate and manage all types of non-complex ocular conditions referred from other departments, clinics and hospitals. The OPD also has different categories of specialist clinics, including retina, cornea, paediatric, glaucoma, neuro-ophthalmology, oculoplastic and uveitis clinics. Cases with ocular conditions that are diagnostic and / or management dilemmas are referred from the general clinic to one of the specialist clinics.

2.2.2 Ophthalmic care in the study population

Ophthalmic cases, including uveitis cases are assessed, investigated and managed initially by the registrar at the general clinic in OPD. All uveitis cases undergo a standard-of-care (SOC) protocol which includes: 1) slit-lamp examination and fundoscopy; and 2) investigations including full blood count and differential, erythrocyte sedimentation rate (ESR), HIV, CD4+ lymphocyte count if HIV-positive, rapid plasma reagin (RPR) and *Treponema pallidum* hemagglutination assay (TPHA), serum angiotensin converting enzyme (sACE) levels, *Toxoplasma* antibodies, antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA) and chest radiograph. If at this stage an aetiological diagnosis is made clinically and /

or by investigative evaluation, then it is treated accordingly. Infective causes of uveitis are treated with antimicrobial agents with or without corticosteroid treatment. Non-infective causes of uveitis are treated with corticosteroid and / or immunosuppressive medication.

Adult uveitis cases that are still undiagnosed after the initial work-up are then referred to the uveitis clinic for assessment, additional investigations and management by a specialist consultant. Additional investigations that may be requested include HLA-B27, HLA-A29, HLA-B51, cerebrospinal (CSF) composition, fluorescein angiogram, optical coherence tomography (OCT) and computed tomography (CT) scan. After excluding all other causes of uveitis, the tuberculin skin test (TST), QFT-TB assay and polymerase chain reaction (PCR) test of ocular fluids (aqueous or vitreous) for viruses and TB are requested.

2.3 Study Design and Method in our Setting: Prospective Cohort Study

2.3.1 Study Design

A prospective cohort study of adult uveitis cases referred from the General Clinic to the Uveitis Clinic at the St John Eye Hospital Outpatients Department (OPD) between June 2014 and November 2018 was undertaken.

2.3.2 Inclusion and Exclusion Criteria (Figure 2.1)

1 Inclusion criteria

1. Age ≥ 18 years.
2. Cases with any clinical signs of active uveitis in one (unilateral) or both (bilateral) eyes.
3. Written consent provided by participants for inclusion in the study.

2 Exclusion criteria

1. Previous or concurrent TB infection.
2. Traumatic uveitis or post-surgical uveitis.
3. Clinically diagnosed uveitis such as acute retinal necrosis (ARN), progressive outer retinal necrosis (PORN), cytomegalovirus (CMV) retinitis, Behcet's disease, Vogt-Koyanagi-Harada (VKH) disease, Fuchs heterochromic iridocyclitis (FHI), sympathetic ophthalmia, birdshot chorioretinopathy, multiple evanescent white dot syndrome (MEWDS), punctate inner choroidopathy (PIC) and acute posterior multifocal placoid pigment epitheliopathy (APMPPE).

4. Uveitis secondary to toxoplasma, syphilis, systemic lupus erythematosus (SLE), polyangiitis with granulomatosis and sarcoid on blood workup and chest radiography.
5. Refusal by participants for ocular fluid (aqueous or vitreous) sampling for PCR testing.

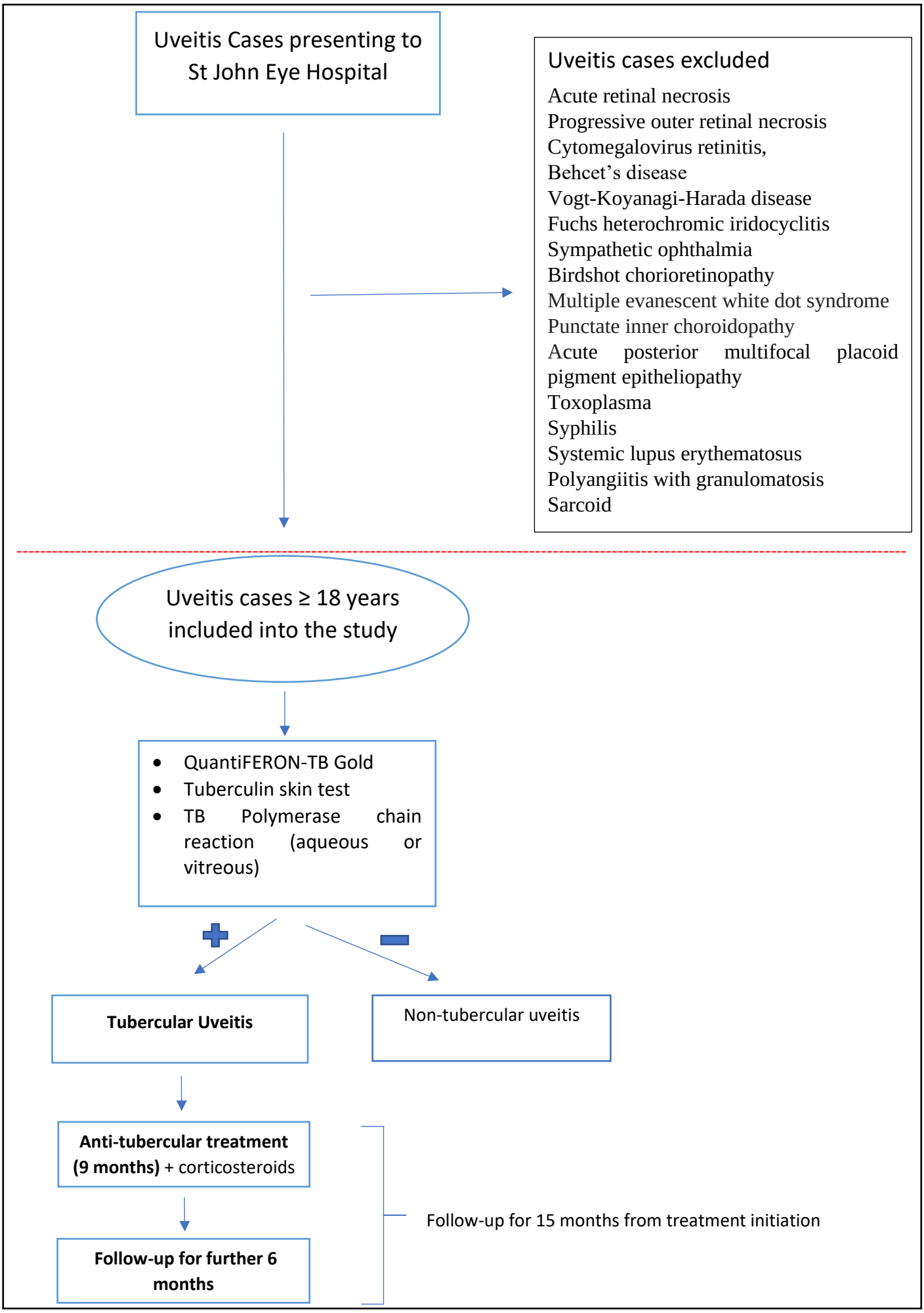


Figure 2.1 Cases included in study for tubercular uveitis investigation and treatment

2.3.3 Study Methods

2.3.3.1 Method for recruitment of case subjects

Case recruitment started on the 14 June 2014 and ended on the 22 November 2018. Uveitis cases referred from the General Clinic to the Uveitis Clinic in OPD at SJEH were approached by me to participate in the study after other aetiological diagnoses of uveitis were excluded based on clinical assessment and / or standard-of-care (SOC) investigations and / or additional investigations (see '2.2.2 Ophthalmic care in the study population'; 2.3.2 'Exclusion criteria' and Figure 2.1 above). These cases were then approached for consent and enrolment into the study (Figure 2.1).

2.3.3.2 Baseline procedures and diagnosis of tubercular uveitis (TBU)

All procedures were conducted by myself.

1. *Procedures conducted at the time of enrolment (Table 2.1):*

- Consent form filled and signed by participant.
- History was recorded, including age, gender, HIV status, TB contact, BCG at birth, duration of uveitis symptoms of the participant was recorded.
- Slit lamp and fundoscopy examination findings were recorded.
- Blood was taken for the QuantiFERON-TB Gold (QFT-G) test to determine interferon-gamma levels released by T cells (this was conducted before the tuberculin skin test (TST)).

  The QFT-G specimen was transported at room temperature within 2 hours to the Lancet laboratory.
- Tuberculin skin test (TST) was performed to determine the delayed-type hypersensitivity immune response in skin.

  The participant was given a date to return in 48 hours to measure the skin reaction to the tuberculin injection.
- Aqueous or vitreous fluid tap was performed on the affected eye in OPD or theatre for TB PCR and viral PCR tests. If the participant had bilateral uveitis (uveitis in both eyes), only one eye (the eye with the worse visual acuity and inflammatory activity) was included for PCR testing.

  Thereafter chloramphenicol eye ointment was placed in the sampled eye, and the eye was covered with an eye pad to be removed by the patient 24 hours

later. Chloramphenicol eye ointment and ciprofloxacin / ofloxacin eye drops were also prescribed to be used daily for one week on removal of the eye pad.

The aqueous or vitreous sample was stored and transported below room temperature to the National Institute for Communicable Diseases (NICD) TB Centre within 3 hours.

2. *Procedures conducted 48 hours later*

- Examination of the sampled eye to rule out any complications.
- Measurement of skin reaction to tuberculin injection.
- Obtaining QuantiFERON-TB Gold (QFT-G) test result.
- Obtaining TB and viral PCR test results, if available (see comment* 1 below).
- Prescribing ATT for cases diagnosed with TBU (based on positive results for any 1, or any combination of, the above 3 tests) (see comment* 2 below). Cases not diagnosed with TBU (based on negative result for all 3 tests) were prescribed corticosteroid medication.
- Notification of cases diagnosed with TBU.

*Comments

1. Regarding the availability of PCR tests at the 48-hour visit: Frequently the PCR tests were not available at this visit - results would usually be available 1 – 2 weeks later. If the TB-PCR test was unavailable and the QFT-G and/or TST were positive at this visit, then the diagnosis of TBU was made, and ATT was prescribed. If both the QFT-G assay and TST were negative, then the diagnosis and decision to prescribe anti-TB would be deferred to the time when the TB-PCR test result became available – this was still regarded as part of the baseline visit.

2. Regarding the diagnosis of TBU: The diagnosis of TBU was made using a composite reference which included: i. any clinical signs of uveitis; ii. other causes of uveitis were excluded; and iii. QFT-G, and/or TST, and/or TB PCR of aqueous or vitreous samples were positive. Participants with positive QFT-G and/or TST were diagnosed with presumed TBU and with positive PCR for TB with confirmed TBU. A TST of $\geq$ 10 mm at 48 hours post intradermal injection, was considered positive in HIV-negative cases; and $\geq$ 5 mm in HIV-positive cases (*Fact Sheets | Testing & Diagnosis | Fact Sheet - Tuberculin Skin Testing | TB |*

CDC, 2020). The TB antigen value minus the negative control value ≥ 0.35 IU/ml in the QFT-G test was considered positive for TBU. The QFT-G was performed before the TST.

Cases that had a negative QFT-G assay, TST and PCR test were diagnosed as non-TBU.

2.3.3.3 Treatment of tubercular and non-tubercular uveitis cases

All diagnosed TBU cases were treated with ATT for 9 months: Rifafour e-275 (Rifampicin [R] 150 mg, Isoniazid [H] 75 mg, Pyrazinamide [Z] 400 mg, and ethambutol hydrochloride [E] 275 mg) for 1st 2 months, and RIFINAH-150 (Rifampicin 150 mg and Isoniazid 100 mg) or RIFINAH-300 (Rifampicin 300 mg and Isoniazid 150 mg) for 7 months; the dose was weight dependent. Topical corticosteroids were prescribed for TBU cases with anterior uveitis; oral and / or periocular corticosteroids for intermediate and posterior uveitis; and oral and / or topical and / or periocular corticosteroids for panuveitis. Periocular steroids were mainly advocated for cystoid macular oedema. Tubercular uveitis cases were followed up for a further 6 months after completion of ATT, totalling 15 months follow-up (Figure 2.1).

All non-TBU cases were treated with topical steroids and/or oral corticosteroid and/or periocular steroids and / or immunosuppressive medication and, also followed-up for 15 months.

All TBU and non-TBU cases were assessed for intraocular inflammation every 1.5 – 3 months for 15 months. Corticosteroid treatment was adjusted at each of the visits according to the activity of the uveitis. Grading of inflammation, activity of uveitis, resolution and remission was defined according to the Standardization of Uveitis Nomenclature (SUN) criteria (Jabs *et al.*, 2005) (see '2.3.3.5 Definitons' below).

Follow-up visits were scheduled from the time the diagnosis was made and treatment initiated (Table 2.1).

Table 2.1 Schedule of visits and procedures on participants in the study

Scheduled visits	Baseline visit	Follow-up Visits					
		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Time period	Enrolment, diagnosis and treatment initiation	1.5 months post diagnosis and treatment initiation	3 months post diagnosis and treatment initiation	6 months post diagnosis and treatment initiation	9 months post diagnosis and treatment initiation	12 months post diagnosis and treatment initiation	15 months post diagnosis and treatment initiation
Informed consent form signed	X						
Inclusion/Exclusion criteria	X						
History	X						
Ocular Examination	X	X	X	X	X	X	X
Blood for QFT-G[1]	X						
Tuberculin skin test	X						
Aqueous or vitreous PCR	X						
Notification of TBU	X						
Anti-tubercular treatment ± corticosteroids[2] for TBU cases	X ±	X ±	X ±	X ±	X ±	±	±
Corticosteroid and/or Immunosuppressive therapy for non-TBU cases	X	±	±	±	±	±	±

[1]QFT-G = QuantiFERON-TB Gold [2]Corticosteroids = If necessary, concomitant corticosteroids were added 2 weeks after initiation of anti-tubercular treatment to control ocular inflammation; in severe inflammation it was prescribed at the same time anti-tubercular treatment was initiated. ± = In the TBU and non-TBU groups, corticosteroids were adjusted according to degree of inflammation.

2.3.3.4 Follow-up visits of tubercular and non-tubercular uveitis cases

All cases had scheduled follow-up visits at 1.5, 3, 6, 9, 12 and 15 months post-diagnosis and treatment initiation (Table 2.1). At these scheduled visits, cases were assessed for ocular inflammation and complications, and side effects to treatment. Depending on the severity of the inflammation, complications and side effects to treatment, ATT and corticosteroid treatment were adjusted accordingly in TBU cases, and corticosteroid and immunosuppressive treatment in non-TBU cases. If necessary and depending on the severity of the ocular inflammation and complications, and side effects to the treatment, cases were assessed between the scheduled visits.

Cases on immunosuppressive treatment had bloods taken for liver function test (LFT), urea & electrolytes (U & E), and Full Blood Count (FBC) & Differential every 1.5 to 3 months to check for hepatotoxicity, nephrotoxicity and bone marrow toxicity, respectively. Cases that failed to attend the scheduled visit within 14 days were denoted as having not attended that visit. Every attempt was made to contact cases (or their next-of-kin) that did not attend follow-up visits.

2.3.3.5 Definitions

1. Grading and activity of uveitis (Table 2.2)

At each follow-up visit the grading and activity outcome of anterior chamber inflammation was according to the standardization of uveitis nomenclature (SUN) criteria (Jabs *et al.*, 2005). At each of these visits the grading of vitreous haze was according to the National Eye Institute system. The activity outcome of vitreous inflammation was according to the SUN criteria (Jabs *et al.*, 2005).

2. Resolution of inflammation

Resolution at each of the follow-up visits in the study was defined as no intraocular inflammation on ≤ 10 mg oral prednisone (Jabs *et al.*, 2005). Participants that had bilateral uveitis were regarded as having achieved resolution when they had no intraocular inflammation in both eyes.

3. Remission

Remission was defined as no inflammatory activity and being on ≤ 10 mg oral prednisone for 6 months duration after completion of 9 months treatment (Jabs *et al.*, 2005). Participants that

had bilateral uveitis were regarded as having achieved remission when they had no intraocular inflammation in both eyes.

Table 2.2 Grading and activity of uveitis

Standardization of Uveitis Nomenclature (SUN) grading scheme for anterior chamber cells (Jabs *et al.*, 2005)]	
Grade	Cells in Field (1mm by 1mm slit beam)
0	<1
0.5+	1-5
1+	6-15
2+	16-25
3+	26-50
4+	>50
National Eye Institute system for grading vitreous haze (Nussenblatt *et al.*, 1985)	
Grade	Haze severity
0	Good view of nerve fibre layer (NFL)
1+	Clear disc and vessel but hazy NFL
2+	Disc and vessel hazy
3+	Only disc visible
4+	Disc not visible
SUN Working Group terminology for activity of uveitis	
Term	Definition
Inactive	Grade 0 cells
Worsening activity	Two-step increase in level of inflammation (e.g., anterior chamber cells, vitreous haze) or increase from grade 3+ to 4+
Improved activity	Two-step decrease in level of inflammation (e.g., anterior chamber cells, vitreous haze) or decrease to grade 0

2.3.4 Laboratory Methods

2.3.4.1 Blood sample collection and processing for the QuantiFERON-TB Gold assay (Figure 2.2)

The QuantiFERON-TB Gold (QFT-G) assay (Cellestis/Qiagen, Carnegie, Australia) was performed as per manufacturer's recommendations. In brief, one millilitre of blood was drawn into each of three tubes: the NIL tube containing no antigens served as a negative control

(blank); the MITOGEN tube containing T-cell mitogen served as a positive control; and the ANTIGEN tube containing *Mycobacterium tuberculosis* complex-specific antigens ESAT-6 (early secreted antigenic target 6), CFP-10 (culture filtrate protein 10) and TB7.7(p4). As the tubes are coated on the inner walls, the tubes were gently inverted several times immediately after drawing blood to ensure the coverage of the entire surface of the inner walls. Thereafter, the tubes were immediately transferred to the laboratory within the specified 16-24 hour at ambient temperature followed by overnight incubation at 37°C for cell stimulation. Following this, the tubes were centrifuged for 15 minutes at 3000 RCF to obtain plasma. A 200 µl aliquot of plasma was taken from each of the tubes and analysed by ELISA to determine the concentration of the interferon-gamma (IFN-γ) released. Interpretation of results was done as described by the manufacturer using the QFT-G Analysis Software (Table 2.3).

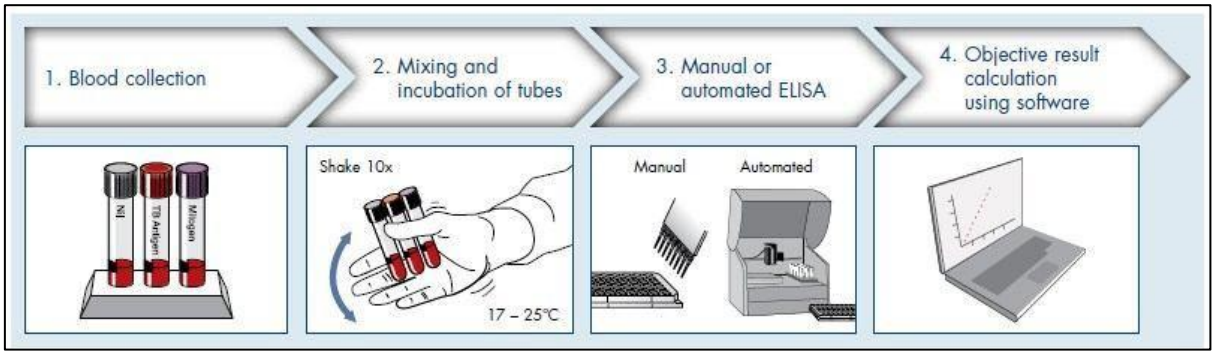


Figure 2.2 Overview of the QFT-G sample process

Table 2.3 Interpretation of Results for the QFT-G assay

Nil (IU/ml)	TB Antigen minus Nil (IU/ml)	Mitogen minus Nil (IU/ml)*	QFT result	Report/Interpretation
≤8.0	< 0.35	≥ 0.5	Negative	*M. tuberculosis* infection NOT likely
	≥ 0.35 and < 25% of Nil value	≥ 0.5	Negative	*M. tuberculosis* infection NOT likely
	≥ 0.35 and ≥ 25% of Nil value	Any	Positive†	*M. tuberculosis* infection likely
	< 0.35	< 0.5	Indeterminate‡	Results are indeterminate for TB-Antigen responsiveness
	≥ 0.35 and < 25% of Nil value	< 0.5	Indeterminate‡	Results are indeterminate for TB-Antigen responsiveness
> 8.0§	Any	Any	Indeterminate‡	Results are indeterminate for TB-Antigen responsiveness

2.3.4.2 Procedure for performing the tuberculin skin test (TST)

The TST was performed by intradermal injection of 0.1 ml of purified protein derivative (PPD) RT 23 (Statens Serum Institute, Copenhagen, Denmark) into the forearm according to the Mantoux technique. The induration was read 48 hours later by me; an induration reactivity of ≥ 10 mm was positive (in PLWH ≥ 5 mm) (Figure 2.3) (*Fact Sheets | Testing & Diagnosis | Fact Sheet - Tuberculin Skin Testing | TB | CDC*, 2020).



Figure 2.3 Colour photograph showing induration reactivity 48 hours after intradermal injection of purified protein derivative (courtesy EyeRounds.org, University of Iowa)

2.3.4.3 Ocular fluid (aqueous or vitreous) sampling procedure and collection

Sampling of ocular fluid from one eye per case was performed under sterile conditions either in the out-patients department (OPD) or in the theatre at St John Eye Hospital. In cases where both eyes were involved, ocular fluid from the more affected eye (poorer VA and worse inflammation) was drawn for analysis. Aqueous fluid sampling was performed at the slit-lamp in OPD. Vitreous fluid sampling was performed in a side room in OPD; in young cases or anxious cases or in cases with a single functioning eye, vitreous fluid sampling was performed in theatre.

Ocular fluid sampling was performed under sterile conditions as follows:

For aqueous fluid sampling, a few drops of a local anaesthetic (lignocaine) were instilled in the eye. Thereafter, a drop of betadine eye drops was placed in the eye 2-3 minutes later. Five minutes later, a 26-gauge needle on a 2 ml syringe was inserted into the aqueous cavity through the limbus, and 0.2 ml of fluid was drawn into the syringe. After removing the needle, a cottonwool bud was used to tamponade the wound to prevent leakage of aqueous fluid.

For vitreous fluid sampling, a few drops of a local anaesthetic (lignocaine) were instilled in the eye. Thereafter, a drop of betadine eye drops was placed in the eye 2-3 minutes later. Five minutes later, a 23-gauge needle on a 2 ml syringe was inserted into the vitreous cavity through the pars plana area (3.5-4 mm behind the limbus), and 0.3-0.4 ml of fluid was drawn into the syringe. After removing the needle, a cottonwool bud was used to tamponade the wound to prevent leakage of vitreous fluid.

Upon completion of either of the two procedures, chloramphenicol (1%) eye ointment was applied to the eye, and an eye pad and eye shield was placed over the eye for 24 hours. Also, chloramphenicol (1%) eye ointment with ciprofloxacin (0.3%) or ofloxacin (0.3%) eye drops were prescribed to be used daily after removal of the eye pad and eye shield.

The ocular fluid samples were placed in a cooler box with ice and transported to the Centre for Tuberculosis, National TB Reference Laboratory (NTBRL) at the National Institute for Communicable Diseases (NICD) within 3 hours. At the NTBRL, the ocular fluid samples were stored at 2-8°C and processed within 48 hours.

2.3.4.4 Laboratory processing of ocular fluid samples

Ocular fluid samples (aqueous or vitreous) received at the NTBRL ranged between 0.2 – 0.4 ml and were processed as follows:

1. Microscopy & Culture

A 10 µl aliquot was processed for smear microscopy by the Auramine-O staining technique. A 50 µl aliquot was used for mycobacterial culture by inoculating mycobacterial growth indicator tubes (MGIT) and incubated on the Bactec MGIT 960 (Becton Dickinson, Sparks, USA) instrument; samples were not decontaminated prior to inoculation as the sample originated from a sterile site.

2. GeneXpert MTB/RIF assay

Processing ocular fluid using the GeneXpert MTB/RIF assay has not been validated. Due to the limited volume of sample, a 50 µl aliquot was used for the GeneXpert MTB/RIF assay deviating from the recommended sample volume and type. To adjust for the low volume, samples were

topped-up with Sample Reagent to a final volume of 2ml (the requirement to load the Xpert cartridge), incubated for 15 minutes with mixing at after 10 minutes. Thereafter, the sample was transferred to the cartridge and loaded into the GeneXpert (Cepheid, Sunnyvale, CA) platform as per manufacturer's instruction.

Due to successive negative results obtained from the GeneXpert assay in the 1st 67 cases, a decision was made to stop further testing as the testing methodology was not optimized for the sample type and the associated cost.

3. Automated DNA extraction

The remaining volume was used for DNA extraction. In brief, DNA was extracted from the remaining sample using the automated Nuclisens EasyMAG (BioMérieux, Marcy-l'Étoile, France) extraction system using the generic protocol with a final DNA elution volume of 50 µl. The extracted DNA was stored at -20°C until further processing.

4. In-house Polymerase Chain Reaction (PCR) for Mycobaterium tuberculosis detection

M. tuberculosis was detected by real-time TB-PCR assays targeting the IS6110 and MPB-64 genes. All primers and probes were designed in-house (Table 2.4) and synthesized by Integrated DNA Technologies, Inc. (www.idtdna.com). For each reaction, 2 µl of DNA was added to a reaction mix containing 10 µl 2x KAPA mastermix, 0.6 µl forward primer [10 µM], 0.6 µl reverse primer [10 µM], 0.6 µl probe [10 µM], 6.2 µl molecular-grade water and 2 µl DNA.

Temperature cycling conditions for both targets were 95°C for 10 minutes, 40 cycles at 95°C for 10 seconds and 40 cycles at 60°C for 32 seconds.

A sample was categorised as *M. tuberculosis* positive/detected if the cycle threshold (Ct) scores was equal to or below 35, indeterminant if the Ct score was above 35 and less than 37 and *M. tuberculosis* negative / not detected if the Ct score was equal to or above 37.

Table 2.4 Primers and probes used for real-time PCR amplification of IS6110 and MPB64

Target	**Primer/Probe**	**Oligonucleotide sequence (5' - 3')**
IS6110	Forward Primer	CTCGTCCAGCGCCGCTTC
	Reverse Primer	ACAAAGGCCACGTAGGCGA
	Probe	/6FAM/ACCAGCACCTAACCGGCTGTGGGTA/MGBNFQ/
MPB64	Forward Primer	GACATTTGAATCTGGCACGC
	Reverse Primer	GCTGTCGTTTTGCTCTGTTG
	Probe	/56-FAM/AGGAGTTGA/Zen/AAGGCACCGATACCG/3IABkFQ/

5. <u>Seeplex Meningitis ACE-V1 (Viral) Detection kit</u>

The Seeplex Meningitis ACE-V1 (Viral) Detection assay (Seegene, Inc., Seoul, South Korea) was performed to detect a viral aetiology that may be related to the uveitis which included detection of several viruses (Herpes Simplex Viruses (HSV1 and 2), Varicella-Zoster Virus (VZV), Epstein-Barr Virus (EBV), Cytomegalovirus (CMV) and Human Herpes Virus 6 [HHV6]) as per manufacturer's instructions. For each reaction, 5 µl of extracted DNA was added to a reaction mix containing 10 µl 2X Multiplex Mastermix, 2 µl 10x MV1 ACE Primer Mixture, 2 µl 8-MOP solution and 1 µl Meningitis ACE Internal Control. PCR amplification was performed in the Bioer Thermal Cycler according to the following conditions: pre-denaturation at 94°C for 15 minutes; denaturation at 94°C for 30 seconds; annealing at 63°C for 90 seconds; 40 cycles of extension at 72°C for 90 seconds and final extension at 72°C for 10 minutes. Agarose gel (2%) electrophoresis was performed using 5 µl of the PCR products using the MV1 ACE amplicon size marker and results interpreted as described by the manufacturer (Figure 2.4).

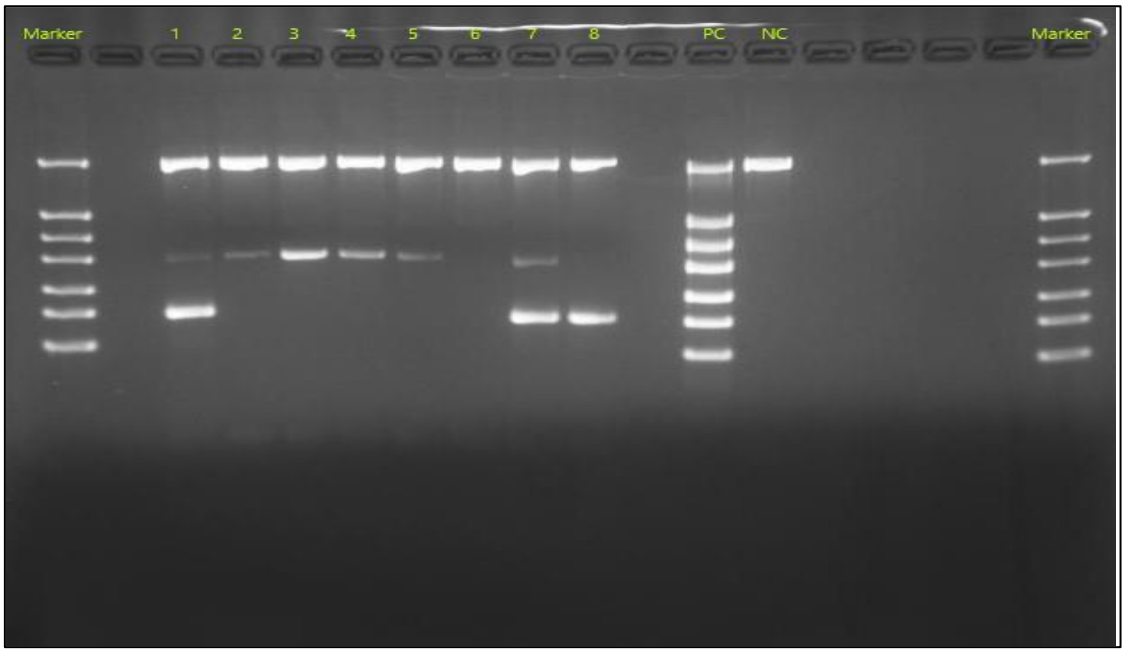


Figure 2.4 Agarose gel (2%) electrophoresis image of DNA amplification

2.3.5 Statistical Analyses

All data were collected and managed using the REDCap (Research Electronic Data Capture) tools hosted at the University of the Witwatersrand (Harris et al., 2009, 2019). Data was analysed in Stata 16.1 (Statacorp, College Station, Texas). Continuous variables were summarized as means (standard deviations) if they were normally distributed and medians (interquartile range) if they were skewed. The comparison of means between the TBU and non-TBU groups was performed using the two-sample t-test. The comparison of medians between the two groups was performed using the Wilcoxon rank-sum test. A chi-squared or Fisher's exact test was used to compare categorical variables.

Univariate logistic regression was used to evaluate the diagnosis of TBU as the outcome with the predictor variables of age, gender, HIV, laterality, TB contacts, BCG at birth, chronicity of uveitis, and clinical signs such as broad-based synechiae, vasculitis, optic neuropathy, serpiginous-like choroiditis, and choroidal granulomas (Chapter 4, Results). The selection of variables in the multivariate logistic regression analysis was done by a stepwise regression method using backward elimination, with significance levels ≤ 0.2 for inclusion (Chapter 4, Results). The estimate of the odds ratio (OR) and its relative 95% confidence interval (CI) were calculated. The models were assessed using receiver operating characteristics (ROC) curves.

Missing data for the longitudinal analysis of resolution was addressed using multiple imputation with chained equations as the pattern of missingness was non-monotone (Chapter 5, Results).

For the longitudinal analysis of resolution as the outcome across all visits we used a two-level multilevel mixed effects model as well as generalized estimating equations, the former to evaluate the individual level response and the latter to evaluate the population level response (Chapter 5, Results). An alpha-level of 0.05 was taken to be statistically significant.

CHAPTER 3 Global Prevalence and Clinical Outcomes of Tubercular Uveitis: A Systematic Review and Meta-analysis

3.1 Background

Worldwide, 7 million new cases of tuberculosis (TB) were reported in 2018, 15% of which were extrapulmonary TB (WHO | Global tuberculosis report, 2019). Intraocular tuberculosis commonly presents independent of the pulmonary manifestation of TB, and frequently (60-93%) presents as tubercular uveitis (TBU) (Donahue, 1967; Biswas and Badrinath, 1995). The prevalence of intraocular TB in individuals with pulmonary TB is between 1.4% to 6.8% (Donahue, 1967; Biswas and Badrinath, 1995; Lara and Ocampo Jr., 2013).

Tubercular uveitis (TBU) can result in ocular morbidity, including visual impairment, chronic hypotony, and blindness (Yeo *et al.*, 2013; Basu *et al.*, 2014; Gunasekeran *et al.*, 2018). Delay in diagnosis, chronic disease, and posterior uveitis with choroiditis are associated with poor visual outcomes (Yeo *et al.*, 2013; Basu *et al.*, 2014; Gunasekeran *et al.*, 2018). The reported prevalence of TBU amongst individuals with uveitis varies from 0.2% to 32% (Kotake *et al.*, 1996; Win *et al.*, 2017). Understanding the pathogenesis of TBU is challenging. The original explanation that TBU results from haematogenous spread and direct invasion of local ocular tissues by *Mycobacterium tuberculosis* (*Mtb*) is oversimplistic. The lack of microbiological or molecular evidence of *Mtb* in ocular samples suggests that an immune reaction to *Mtb* antigens or nonviable *Mtb* bacilli in the eye may play a role (Wroblewski *et al.*, 2011; Forrester *et al.*, 2013; Basu, Elkington and Rao, 2020). Another possible explanation is that TBU is an autoimmune reaction whereby distal T-cell priming occurs due to a cross-reaction between *Mtb* and retinal antigens (Garip *et al.*, 2009; Basu, Elkington and Rao, 2020).

The clinical signs suggestive of TBU described are broad-based posterior synechiae, severe vitritis, retinal vasculitis, serpiginous-like choroiditis, choroidal granuloma and choroidal abscess (Babu *et al.*, 2006; Gupta *et al.*, 2010; Ang *et al.*, 2012a). More recently, the Collaborative Ocular Tuberculosis Study (COTS) identified serpiginous-like choroiditis and choroidal granulomas as being strongly associated with TBU in endemic and non-endemic regions (Agrawal *et al.*, 2020a). Detection of *Mtb* by microscopy, culture or polymerase chain reaction (PCR) of ocular fluids (aqueous or vitreous humour) is the definitive method for diagnosing TBU (Gupta, Gupta and Rao, 2007; Yeh *et al.*, 2012). Currently, PCR is the method of choice to diagnose TBU. In single-centre studies, the PCR-positivity rate in TBU cases is between 37.7-58.8% (Gupta *et al.*, 1998; Arora *et al.*, 1999; Sudheer *et al.*, 2018). In the COTS multicentre study, the reported TBU PCR-positivity rate was 55.9% (Agarwal *et al.*, 2019). In

one study using multi-targeted PCR, where several genes (*IS6110, MPB64* and *protein b*) were simultaneously amplified, the PCR-positivity rate in TBU cases was reportedly higher (77.8%) (Sharma *et al.*, 2013). The variable and inconsistent diagnostic accuracy of PCR, and the possible 'immune mediated' pathogenesis of TBU have led to the use of indirect immunological tests, such as the tuberculin skin test (TST) and interferon-gamma release assay (IGRA), in supporting the diagnosis of TBU (Llorenç *et al.*, 2013). These tests, however, have low sensitivities and specificities, and are unable to discriminate between latent and active TB (Huebner, Schein and Bass, 1993; Babu *et al.*, 2009b; Ang, Htoon and Chee, 2009). Chest and ocular imaging rarely assist in making the diagnosis of TBU (Gupta, Gupta and Rao, 2007; Alvarez, Roth and Hodge, 2009; Vasconcelos-Santos, Zierhut and Rao, 2009). Since diagnostic tests are not singularly helpful, the diagnosis of TBU is often based on different combinations of the above investigations, together with suggestive clinical findings and clinical response to anti-tubercular treatment (ATT) (Gupta, Gupta and Rao, 2007; Vasconcelos-Santos, Zierhut and Rao, 2009; Gupta *et al.*, 2015). The lack of standardization in the diagnostic criteria of TBU, and the poor reliability of laboratory methods have contributed to the large variations in the reported prevalence of TBU (Gupta, Gupta and Rao, 2007).

The clinical outcomes, specifically the clinical response to ATT, during treatment and after its completion, is usually determined by measuring the improvement or resolution of inflammation in the eye. Variable clinical responses to ATT, as low as 24% and as high as 100%, have been reported (Ang *et al.*, 2012b; Manousaridis *et al.*, 2013; Shakarchi, 2015a). Tubercular uveitis patients treated for 9 months or longer have been reported to have better clinical outcomes than those treated for 6 months (Ang *et al.*, 2012b; Agrawal *et al.*, 2015). Low-dose systemic and / or topical corticosteroids are often used in combination with multi-drug ATT, to control the inflammation and limit the damage to ocular tissues.

There is a paucity of literature on the prevalence of TBU globally. Furthermore, a systematic review on treatment outcomes for intraocular TB following ATT conducted in 2016 (Kee *et al.*, 2016) did not analyze the effect of different anti-TB drug regimens on treatment outcome of TB. Also, the review, whilst stratifying analyses between Asian and non-Asian countries, did not compare the outcome of TBU between countries with a high burden of TB (HBCs) and non-HBCs, or between the 7 super-regions defined by the Global Burden of disease (GBD) study (Murray *et al.*, 2012; Vos *et al.*, 2020).

We undertook a systematic review and meta-analysis on the prevalence of TBU diagnosis in individuals presenting with uveitis; and the clinical outcomes of TBU. We aimed to determine:

i. the overall prevalence of TBU, including stratification between HBCs and non-HBCs, between different GBD geographic regions, and between studies with data collection started before 2010 and studies with data collection started during or after 2010. ii. the response of TBU to ATT, including stratification between HBCs and non-HBCs. The year 2010 was arbitrarily chosen on the assumption that the 2007 Gupta and coworkers TBU diagnostic criteria would have been in widespread use by then (Gupta, Gupta and Rao, 2007).

3.2 Methods

3.2.1 Search methods for identifying studies

A literature search of PubMed, EMBASE and Scopus databases was last conducted on 1 July 2020 using the search terms detailed in Table 3.1. The search included English and other-language publications. However, full non-English publications that were not translated to English were excluded. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (Moher *et al.*, 2009) checklist and flow diagram were used to identify, screen and exclude studies (Figure 3.1). A reference manager, Zotero, was used to import the titles of all the studies from the 3 databases. Duplicate titles were manually removed.

3.2.2 Study selection

All titles and abstracts were reviewed by 2 authors (HDA and IM), with a third author (SAM) adjudicating on conflicting results. Systematic and narrative reviews, animal studies, editorials and letters were excluded. However, the reference lists of review papers were screened for studies that met inclusion criteria. The full texts of eligible studies / papers were then examined for inclusion into the prevalence or clinical outcome parts of the systematic review and meta-analysis. When data from the same cohort were reported in separate manuscripts, the study reporting the largest sample fulfilling our eligibility criteria was selected. If there were doubts regarding these datasets, contact with the corresponding authors was attempted for clarification.

3.2.3 Eligibility criteria for considering studies for this review

All studies published prior to and until 30 June 2020 were included if they: i. had ≥ 20 uveitis cases for prevalence estimates of TBU, or ≥ 5 uveitis cases for clinical outcomes; ii. described patients of all ages; iii. included all anatomical classification types (anterior, intermediate, posterior and panuveitis); iv. reported the prevalence of TBU in a population of uveitis cases, and for clinical outcomes, reported the response of inflammatory activity after completion of ATT in TBU cases. Studies were excluded for description of TBU prevalence among uveitis cases if: i. it exclusively assessed HIV positive or negative patients; ii. limited to a specific patient population and exclusion of others based on race or ethnicity; and iii. data were missing or did not correlate within the same publication. For clinical outcomes, studies were excluded if: i. clinical (inflammatory) outcome to ATT was part of the diagnostic criteria for TBU in the same study; and ii. data were missing or did not correlate within the same publication.

3.2.4 Data collection and risk of bias assessment

Two authors (HDA and NA) extracted the data with disagreements resolved through discussion. Disagreements that persisted were resolved by a third author (IM). Data were extracted according to the aims of the systematic review and meta-analysis. Since we also determined the prevalence i. in high quality studies, ii. based on diagnostic criteria, iii. based on study design; and the clinical outcomes on different anti-TB drug regimen and treatment duration, the data were extracted accordingly. For prevalence, the following data were extracted from published studies: author, year, country, study design, total number of uveitis patients, mean age and standard deviation of uveitis patients, sex of uveitis patients, number of TBU patients, diagnostic criteria with or without ATT and data quality (Table 3.2). For clinical outcomes, the following data were extracted from published studies: author, year, country, study design, mean age and standard deviation of TBU patients, sex of TBU patients, number of TBU patients treated, number of TBU patients that responded to ATT, anti-TB drugs, ATT duration and data quality (Table 3.3). The studies were classified as HBC or non-HBC for TB according to the World Health Organization (WHO) TB burden data (*WHO | Global tuberculosis report, 2019*).The studies were divided into 7 GBD super-regions: 1. High Income (North America, Southern Latin America, Western Europe, Asia-Pacific and Australasia), 2. Central Europe, Eastern Europe and Central Asia, 3. East Asia, South-East Asia and Oceania, 4. South Asia, 5 North Africa and Middle East, 6. Sub-Saharan Africa, and 7. Latin America and Caribbean (Murray *et al.*, 2012; Vos *et al.*, 2020). The division of studies according to when data collection was started (before 2010 or during and after 2010) was arbitrary and based on the assumption that the criteria suggested by Gupta and coworkers would have taken a while to be applied to the studies before starting data collection (Gupta, Gupta and Rao, 2007). Extracted data were stored in Microsoft Excel™ (Microsoft Corporation).

The quality and risk of bias of the included studies were assessed using a modified version of the Joanna Briggs Institute (JBI) critical appraisal tool (Munn *et al.*, 2015; Moola S *et al.*, 2017). The assessment scales were adapted to the relevant questions under review and are shown in Table 3.4. HDA and NA independently rated the quality of the studies with disagreements resolved through discussion and where necessary a third author (IM).

3.2.5 Data synthesis and analysis

Statistical analysis was performed using STATA 16.1 (Statacorp LLC, College Station, Texas). A random-effects model was used to perform the meta-analysis. Sub-groups were specified prior to statistical analysis based on TB high-burden countries (HBCs) and non-HBCs; geographical regions; studies with data collection started before 2010 and during or after 2010; study design; diagnostic criteria; and anti-TB drug regimen in terms of number of drugs and duration of ATT. Binary outcome data were analyzed using the "metaprop" command in STATA, and reported as proportions. The Freeman-Tukey double arcsine transformation was performed to normalize outcomes before pooling the prevalence. Study specific 95% confidence intervals were generated using the exact method. The I^2 statistic was used to check for overall, intergroup, and intragroup heterogeneity, and was classified as

not important (0-40%), moderate (30-60%), substantial (50-90%) and considerable (75-100%) using the Cochrane guide (*Chapter 10: Analysing data and undertaking meta-analyses*). Forest plots were then generated from the data. When the subanalysis was conducted for treatment outcome according to number of drugs or treatment duration, studies that did not indicate the number of drugs or treatment duration were excluded from this sub-analysis. The weighted mean age was calculated using the "meta set" command and restricted maximum likelihood, from studies that provided a mean age and standard deviation, in addition to the total number of uveitis patients for prevalence and the total number of TBU for clinical outcomes. The weighted proportion of males to females was calculated using the "metaprop" command as stated above.

3.3 Results

3.3.1 Search results

Of 5018 articles identified through the 3 database searches (Figure 3.1), 280 articles were assessed for eligibility and 85 articles (70 for prevalence and 18 for clinical outcome) were included. Three studies with clinical outcome data also contributed to data on prevalence of TBU in uveitis cases (Manousaridis *et al.*, 2013; Shakarchi, 2015a; Ng *et al.*, 2017) (Table 3.2). All the studies reporting on prevalence of TBU were hospital-based, and 3 studies had sets of data from different time periods all of which were included (Kotake *et al.*, 1996; Siak *et al.*, 2017; Kunimi *et al.*, 2020) (Table 2). All 18 studies reporting on clinical outcomes were hospital-based (Table 3.3).

3.3.2 Studies reporting on prevalence of tubercular uveitis (TBU)

Of the 70 studies reporting on prevalence of TBU, 50 (71%) were case series, 10 (14%) cross-sectional, 9 (13%) cohort studies and 1 (2%) a case-control study (Table 3.2). Twenty-five (36%), 29 (41%) and 13 (19%) of the studies were of high, medium, and low quality, respectively (Table 3.2). Twenty-two studies (31%) were from TB HBCs (including 8 from India), and 48 (69%) studies were from non-HBCs, of which 5 each were from Japan and Saudi Arabia (Table3.2 and Figure 3.2). Twenty-seven studies were from countries in the High-Income region (North America, Western Europe, Asia-Pacific, Australasia and Southern Latin America), 10 from the East Asia, South-East Asian and Pacific region, 11 from the South Asia region, 17 from the North Africa-Mediterranean region, 2 from the sub-Saharan Africa region, and 2 from the Latin America and Caribbean region (Table 3.2 and Figure 3.3). Data collection was started before 2010 in 53 studies, and during or after 2010 in 19 studies (Figure 3.4); 2 studies (Siak and coworkers[100] and Kunimi and coworkers[69]) had 2 sets of data, of which 1 was collected before 2010, and the other during or after 2010 (Siak *et al.*, 2017; Kunimi *et al.*, 2020). Of the 25 high-quality studies, 18 were from non-HBCs and 7 were from HBCs (Figure 3.5).

Nineteen studies had no diagnostic criteria for TBU. (Rahimi and Mirmansouri, 2014; Kotake *et al.*, 1996; Rodriguez *et al.*, 1996; Thean, Thompson and Rosenthal, 1996; Sengün *et al.*, 2005; Yang *et al.*, 2005; Goto *et al.*, 2007; Rathinam and Namperumalsamy, 2007; Kazokoglu *et al.*, 2008; Jakob *et al.*, 2009; Roy, 2014; Çakar Özdal *et al.*, 2014; Das *et al.*, 2015; Engelhard *et al.*, 2015; Jones, 2015; Schaftenaar *et al.*, 2016; Teixeira *et al.*, 2016; Gonzalez Fernandez *et al.*, 2017; Lee *et al.*, 2017) There were 18 studies that had diagnostic criteria that included response to ATT (Islam and Tabbara, 2002; Singh, Gupta and Gupta, 2004; Hamade, Elkum and Tabbara, 2009; Ball *et al.*, 2010; Nora *et al.*, 2012; Vos *et al.*, 2013; Nizamuddin and Bawazeer, 2013; Tognon *et al.*, 2014; Abdulaal *et al.*, 2015; Al Dhahri *et al.*, 2015; Liberman *et al.*, 2015; Al Dhibi *et al.*, 2017; Chen *et al.*, 2017, 2018; Gao *et al.*, 2017; Siak *et al.*, 2017; Win *et al.*, 2017; Al-Baker, Bodaghi and Khan, 2018); only 4 (22.2%) of these studies (Singh, Gupta and Gupta, 2004; Tognon *et al.*, 2014; Chen *et al.*, 2017; Siak *et al.*, 2017) had microbiological / molecular analysis of intraocular fluid as part of the diagnostic criteria. Twenty-nine studies (Biswas *et al.*, 1996; Merrill *et al.*, 1997; Soheilian *et al.*, 2004; Khairallah *et al.*, 2007; Das *et al.*, 2009; Keino *et al.*, 2009; Miyanaga *et al.*, 2009; Manousaridis *et al.*, 2013; Sittivarakul, Bhurayanontachai and Ratanasukon, 2013; Yeo *et al.*, 2013; Ang *et al.*, 2014a; Shakarchi, 2015a; Grajewski *et al.*, 2015; Kianersi *et al.*, 2015; Kilic *et al.*, 2015; Silpa-Archa, Noonpradej and Amphornphruet, 2015; Zheng *et al.*, 2015; Manandhar, 2017; Dogra *et al.*, 2017; Ng *et al.*, 2017; Sukavatcharin *et al.*, 2017; Wong *et al.*, 2017; Zagora *et al.*, 2017; Brydak-Godowska *et al.*, 2018; Biswas, Kharel Sitaula and Multani, 2018; Rahman *et al.*, 2018; Abd El Latif and Ammar, 2019; Borde *et al.*, 2020; Kunimi *et al.*, 2020) had diagnostic criteria, but did not include response to ATT, 11 (38%) (Biswas *et al.*, 1996; Soheilian *et al.*, 2004; Manousaridis *et al.*, 2013; Grajewski *et al.*, 2015; Manandhar, 2017; Dogra *et al.*, 2017; Ng *et al.*, 2017; Sukavatcharin *et al.*, 2017; Biswas, Kharel Sitaula and Multani, 2018; Rahman *et al.*, 2018; Kunimi *et al.*, 2020) of which had microbiological / molecular analysis of intraocular fluid as part of the diagnostic criteria. Four studies (Llorenç *et al.*, 2015; Abaño *et al.*, 2017; Pandey *et al.*, 2018; Rautenbach *et al.*, 2019) used criteria mentioned in the review articles by Gupta and coworkers (Gupta, Gupta and Rao, 2007; Gupta *et al.*, 2015), albeit it being unclear as to which criteria were used.

Table 3.1 Search strategy and terms

	Tuberculosis AND Uveitis AND Diagnosis
OR	(("Diagnosis"[Mesh]) AND "Tuberculosis"[Mesh]) AND "Uveitis"[Mesh]
OR	Tuberculosis Uveitis AND Diagnosis
OR	Diagnosis of Tuberculous Uveitis
OR	TB Uveitis AND Diagnosis
OR	Diagnosis of TB Uveitis
OR	Tuberculosis AND Uveitis AND Treatment
OR	(("Tuberculosis" [MESH] AND "Uveitis" [MESH]) AND "Treatment outcome" [MESH]
OR	Tuberculous Uveitis AND Treatment Outcomes
OR	TB Uveitis AND Treatment Outcomes
OR	Tuberculosis AND Uveitis
OR	(("Tuberculosis"[MESH]) AND "Uveitis" [MESH]
OR	Tuberculous Uveitis
OR	TB Uveitis
OR	TB AND Uveitis
OR	Tuberculosis AND Ocular Inflammation
OR	Tuberculous Ocular Inflammation
OR	TB AND Ocular Inflammation’
OR	Tuberculous Uveitis AND Prevalence
OR	Tuberculous Uveitis AND Incidence

Table 3.2 Study characteristics of prevalence studies

	Study author (year)	Study design	R/P[1]	Country of study	HBC[2] yes/no	Uveitis patients; n	Mean Age in years	SD[3]	Sex Male n (%)	TB uveitis patients n	Diagnostic criteria used yes/no	ATT[4] yes/no	Data Quality Low/Med[5]/High
1	Biswas *et al*. (1996)	Case series	R	India	Yes	1273			792 (62)	7	Yes	No	Med
2	Kotake* *et al*. (1996)	Case series	R	Japan	No	407	40·7		179 (44)	1	No	No	Med
		Case series	R	Japan	No	551	46·5		237 (43)	1	No	No	Med
3	Thean, Thompson and Rosenthal (1996)	Case series	R	UK	No	712	39·2		371 (52)	2	No	No	Med
4	Rodriguez *et al.* (1996)	Case series	R	USA	No	1237	39·8	16·2	512 (41)	8	No	No	Med
5	Merrill *et al.* (1997)	Case series	R	USA	No	385			148 (38)	2	Yes	No	High
6	Islam and Tabbara (2002)	Case series	R	Saudi Arabia	No	200	38	16	120 (60)	21	Yes	Yes	High
7	Singh, Gupta and Gupta (2004)	Case series	R	India	Yes	1233			641 (52)	125	Yes	Yes	Med
8	Soheilian *et al.* (2004)	Cross-sectional		Iran	No	544	34·3	15·4	238 (44)	8	Yes	No	High
9	Sengün *et al.* (2005)	Case series	R	Turkey	No	300	35·7		162 ((54)	4	No	No	Med

10	Yang *et al.* (2005)	Case series	R	China	Yes	1752	33·8	16·5	902 (52)	13	No	No	Med
11	Goto *et al.* (2007)	Cross-sectional		Japan (Multicentre)	No	3060				20	No	No	Low
12	Khairallah *et al.* (2007)	Cohort	R	Tunisia	No	472			224 (47)	5	Yes	No	High
13	Rathinam and Namperumalsamy (2007)	Case series	R	India	Yes	8759	36·5	15·5	5451 (62)	488	No	No	Low
14	Kazokoglu *et al.* (2008)	Cross-sectional		Turkey (Multicentre)	No	761	35·4	15·3	388 (51)	3	No	No	Low
15	Das *et al.* (2009)	Case series	R	India	Yes	308			209 (68)	9	Yes	No	High
16	Hamade, Elkum and Tabbara (2009)	Case series	R	Saudi Arabia	No	488	38		264 (54)	37	Yes	Yes	High
17	Jakob *et al.* (2009)	Case series	R	Germany	No	1686			752 (45)	21	No	No	Low
18	Keino *et al.* (2009)	Case series	R	Japan	No	834			352 (42)	36	Yes	No	High
19	Miyanaga *et al.* (2009)	Case series	R	Japan	No	1338	50·5	17·7	526 (39)	5	Yes	No	High
20	Ball *et al.* (2010)	Cross-sectional		France	No	108	49·4	19·1		13	Yes	Yes	High
21	Nora *et al.* (2012)	Case series	R	Indonesia	Yes	1004				39	Yes	Yes	Med
22	Manousaridis *et al.* (2013)	Cohort	R	UK	No	1360				21	Yes	No	¶
23	Nizamuddin and Bawazeer (2013)	Case series	R	Saudi Arabia	No	587	34·8	12·8	319 (54)	6	Yes	Yes	Med

24	Sittivarakul, Bhurayanontachai and Ratanasukon, (2013)	Case series	R	Thailand	Yes	254	42·6	17	140 (55)	3	Yes	No	High
25	Vos *et al.* (2013)	Case series	R	Netherlands	No	575				11	Yes	Yes	Med
26	Yeo *et al.* (2013)	Case series	R	Singapore	No	359			206 (57)	24	Yes	No	High
27	Ang *et al.* (2014a)	Cohort	P	Singapore	No	102	48·2	16·7		23	Yes	No	High
28	Çakar Özdal *et al.* (2014)	Case series	R	Turkey	No	1028	36·2	14·9	598 (58)	6	No	No	Low
29	Rahimi and Mirmansouri (2014)	Cross-sectional		Iran	No	475	30·5	15·14	216 (45)	2	No	No	Med
30	Roy (2014)	Case-control	R	Canada	No	43	32·1	15·4	9 (21)	2	No	No	Low
31	Tognon *et al.* (2014)	Cohort	P	Italy	No	351				45	Yes	Yes	Med
32	Abdulaal *et al.* (2015)	Case series	R	Lebanon	No	209	36	18	91 (44)	12	Yes	Yes	High
33	Al Dhahri *et al.* (2015)	Case series	R	Saudi Arabia	No	642	36·4	16·1	295 (46)	114	Yes	Yes	High
34	Das *et al.* (2015)	Case series	R	India	Yes	343			209 (61)	60	No	No	Low
35	Engelhard *et al.* (2015)	Cohort	R	USA	No	491				1	No	No	Med
36	Grajewski *et al.* (2015)	Case series	R	Germany	No	474			213 (45)	1	Yes	No	High
37	Jones (2015)	Case series	R	UK	No	3000			1377 (46)	99	No	No	Low

38	Kianersi *et al.* (2015)	Case series	R	Iran	No	2016	33·8	10·56	915 (45)	4	Yes	No	High
39	Kilic *et al.* (2015)	Case series	R	Turkey	No	140	39·6	14·9	79 (56)	1	Yes	No	Med
40	Liberman *et al.* (2015)	Case series	R	Chile	No	611			256 (42)	14	Yes	Yes	Med
41	Llorenç *et al.* (2015)	Cross-sectional		Spain	No	1022			465 (46)	54	Gupta		Low
42	Shakarchi (2015a)	Cohort	P	Iraq	No	506				64	Yes	No	¶
43	Silpa-Archa, Noonpradej and Amphornphruet (2015)	Case series	R	Thailand	Yes	446	42·6	16·1	206 (46)	10	Yes	No	Med
44	Zheng *et al.* (2015)	Case series	R	China	Yes	199	41	15·1	134 (67)	2	Yes	No	High
45	Schaftenaar *et al.* (2016)	Cross-sectional		South Africa (Multicentre)	Yes	103			37 (36)	18	No	No	Low
46	Teixeira *et al.* (2016)	Case series	R	Brazil	Yes	403			199 (49)	12	No	No	Med
47	Abaño *et al.* (2017)	Case series	R	Philippines	Yes	595	38·5	18·9	271 (0.45)	70	Gupta		Low
48	Al Dhibi *et al.* (2017)	Cohort	R	Saudi Arabia	No	888			390 (44)	94	Yes	Yes	Med
49	Chen *et al.* (2017)	Case series	R	Taiwan	No	450	41·7	15·9	240 (53)	3	Yes	Yes	Med
50	Dogra *et al.* (2017)	Case series	R	India	Yes	1807			1046	438	Yes	No	High

									(58)				
51	Gao *et al.* (2017)	Case series	R	China	Yes	606	33·8	15·5	291 (48)	11	Yes	Yes	High
52	Gonzalez Fernandez *et al.* (2017)	Cross-sectional		Brazil	Yes	1053	39·8	17·8	455 (43)	55	No	No	Med
53	Lee *et al.* (2017)	Case series	R	South Korea (Multicentre)	No	602	45·1	16·5	314 (52)	10	No	No	Low
54	Manandhar (2017)	Case series	R	Nepal	No	1113			567 (51)	45	Yes	No	Med
55	Ng *et al.* (2017)	Cohort	R	New Zealand	No	1207				39	Yes	No	¶
56	Siak* *et al.* (2017)	Case series	R	Singapore	No	1249	45·8	16	639 (51)	84	Yes	Yes	High
		Case series	P	Singapore	No	148			80 (54)	6	Yes	Yes	High
57	Sukavatcharin *et al.* (2017)	Cross-sectional		Thailand	Yes	758	45·6	16·6	357 (47)	65	Yes	No	Med
58	Win *et al.* (2017)	Case series	R	Myanmar	Yes	139			71 (51)	45	Yes	Yes	High
59	Wong *et al.* (2017)	Case series	R	New Zealand	No	1148			621 (54)	36	Yes	No	Med
60	Zagora *et al.* (2017)	Case series	R	Australia (Multicentre)	No	1165	51		650 (56)	49	Yes	No	High
61	Al-Baker, Bodaghi and Khan (2018)	Case series	R	Qatar	No	310	39·3	14·2	186 (60)	45	Yes	Yes	High

62	Biswas, Kharel Sitaula and Multani (2018)	Case series	R	India	Yes	352				79	Yes	No	Med
63	Brydak-Godowska *et al.* (2018)	Case series	R	Poland	No	279	38·3	15·3	107 (38)	2	Yes	No	Med
64	Chen *et al.* (2018)	Case series	R	Singapore	No	1978			1185 (60)	148	Yes	Yes	High
65	Pandey *et al.* (2018)	Cohort	P	Nepal	No	1140				12	Gupta		Med
66	Rahman *et al.* (2018)	Case series	R	Bangladesh	Yes	652	32·3	12·4	340 (52)	70	Yes	No	High
67	Abd El Latif and Ammar (2019)	Case series	R	Egypt	No	1315	34·8	11·9	702 (53)	202	Yes	No	Med
68	Rautenbach *et al.* (2019)	Case series	R	South Africa (Multicentre)	Yes	198	38		93 (47)	16	Gupta		Low
69	Borde *et al.* (2020)	Cross sectional		India	Yes	210	46·6	11·2	107 (51)	25	Yes	No	Med
70	Kunimi* *et al.* (2020)	Case series	R	Japan	No	1507			697 (46)	21	Yes	No	Med
		Case series	R	Japan	No	1587			707 (45)	19	Yes	No	Med

[1]R/P = Retrospective/Prospective; [2]HBC = High-burden-country for TB defined by the WHO (*WHO | Global tuberculosis report, 2019*); [3]SD = standard deviation; [4]ATT = anti-tubercular treatment; [5]Med = medium

Data quality: Assessment of quality of study for prevalence modified from the Joanna Briggs Institute (JBI) critical appraisal tool (Munn *et al.*, 2015).

Gupta criteria: Diagnostic criteria according to Gupta et al's. review articles (Gupta, Gupta and Rao, 2007; Gupta *et al.*, 2015) but criteria not specified in these studies.

* Studies with two data sets

¶ Studies rated for clinical outcomes (see table 3.3)

Table 3.3 Study characteristics of Clinical outcome studies

	Study author (year)	Study design	R/P[1]	Country of study	HBC[2]	All TBU[3]	Mean age All TBU[3]	SD[4] All TBU[3]	Sex Male All TBU[3]	Number of TBU[3] patients treated	Number of TBU[3] patients responded to treatment	Intensive phase ATT[5] drugs R[6]/H[7]/Z[8]/E[9]/M[10]	Total ATT[5] Duration (months)	Data Quality Low/Med[11]/High
1	Gupta *et al.* (1998)	Cohort	P	India	Yes					10	9	RHZ	≥ 9	Med
2	Babu *et al.* (2009a)	Cohort	R	India	Yes	51	40·5	11·5	27	49	41	RHZE	≥ 9	Med
3	Sanghvi *et al.* (2011)	Cohort	R	UK	No	45				27	19	RHZE	6	Med
4	Ang *et al* (2012b)	Cohort	R	Singapore	No					46	11	RHZE	Varied	Med
6	Manousaridis *et al.* (2013)	Cohort	R	UK	No	21	46		15	16	16	RHZE	6	Med
6	Balne *et al.* (2014)	Cohort	R	India	**Yes**	114	33·7	12·7	71	71	65	~~Ŧ~~	6	Med
7	Agrawal *et al.* (2015)	Cohort	R	UK	No	375				175	135	RHZE or RHZM	Varied	Med
8	Shakarchi (2015a)	Cohort	P	Iraq	No	64	35·7		29	64	64	RHZE	6	High
9	Agrawal *et al.* (2017a)	Cohort	R	Multicentre (COTS-1)		801	40·5	14·8	413	801	699	~~Ŧ~~	ǂ	High
10	Damato *et al.* (2017)	Cohort	R	UK	No	54	44		33	41	33	RHZE or RHZ or RZE or RH or RE	Varied	Med
11	Ng *et al.* (2017)	Cohort	R	New Zealand	No	39			17	24	16	RHZE or RHZM or RHZ	Varied	Med
12	Ang *et al.* (2018)	Cohort	R	Singapore	No	62				36	25	RHZE	Varied	Med
13	Anibarro *et al.* (2018)	Cohort	R	Spain	No	*24*	48·3	10·6	15	23	21	3- or 4-drug ATT	6	Med

14	Chung and Li (2018)	Cohort	R	China	Yes					14	13	RHZE	Varied	High
15	Krassas *et al.* (2018)	Cohort	R	UK	No	91				48	29	RHZE	6	Med
16	Sudheer *et al.* (2018)	Cohort	R	India	Yes					34	30	RHZE	6	Med
17	Ghauri *et al.* (2019)	Cohort	P	Pakistan	Yes	40	36	3	16	40	32	RHZE	≥ 9	High
18	Llorenç *et al.* (2020)	Cohort	R	Spain	No	93				51	46	RHZE	Varied	Med

[1]R/P =Retrospective/Prospective; [2]HBC = High-burden country for TB defined by the WHO (*WHO | Global tuberculosis report, 2019*); [3]TBU = Tubercular uveitis; [4]SD = standard deviation; [5]ATT = anti-tubercular treatment; [6]R = Rifampicin; [7]H = Isoniazid; [8]Z = Pyrazinamide; [9]E = Ethambutol; [10]M = Moxifloxacin; [11]Med = medium

Data quality = Assessment of quality of study for clinical outcome modified from the Joanna Briggs Institute (JBI) critical appraisal tool (Moola S *et al.*, 2017).

Varied = studies in which ATT duration was < 9 months in some patients and ≥ 9 months in others.

Ŧ = Number and names of ATT drugs not stated in study.

ǂ = ATT duration not stated in study.

Table 3.4: Assessment of quality of the studies modified from the Joanna Briggs Institute (JBI) critical appraisal tools (Munn *et al.*, 2015; Moola S *et al.*, 2017).

Prevalence

		Yes	No
1	Were study subjects and setting described in detail?		
2	Were valid methods used for the identification of the condition?		
3	Was the condition measured in a standard, reliable way for all participants?		
4	Did the study have consecutive inclusion of participants?		
5	Did the study have complete inclusion of participants?		
6	Was there clear reporting of the demographics of the participants in the study?		
7	Was there clear reporting of the prevalence numbers (%) of the condition?		

Quality: 0-3 = Low 4-5 = Medium 6-7 = High

Clinical outcome

		Yes	No
1	Were there clear criteria for inclusion in the study?		
2	Were valid methods used for the identification of the condition?		
3	Was the condition measured in a standard, reliable way for all participant?		
4	Did the study have consecutive inclusion of participants?		
5	Did the study have complete inclusion of participants?		
6	Was there clear reporting of the demographics of the participants in the study?		
7	Was there clear reporting of clinical information of the participants?		
8	Were the outcomes or follow-up results of cases clearly reported?		
9	Was there clear reporting of the presenting site(s)/hospital(s)?		
10	Specific anti-TB drugs used and duration of treatment?		

Quality: 0-3 = Low 4-7 = Medium 8-10 = High

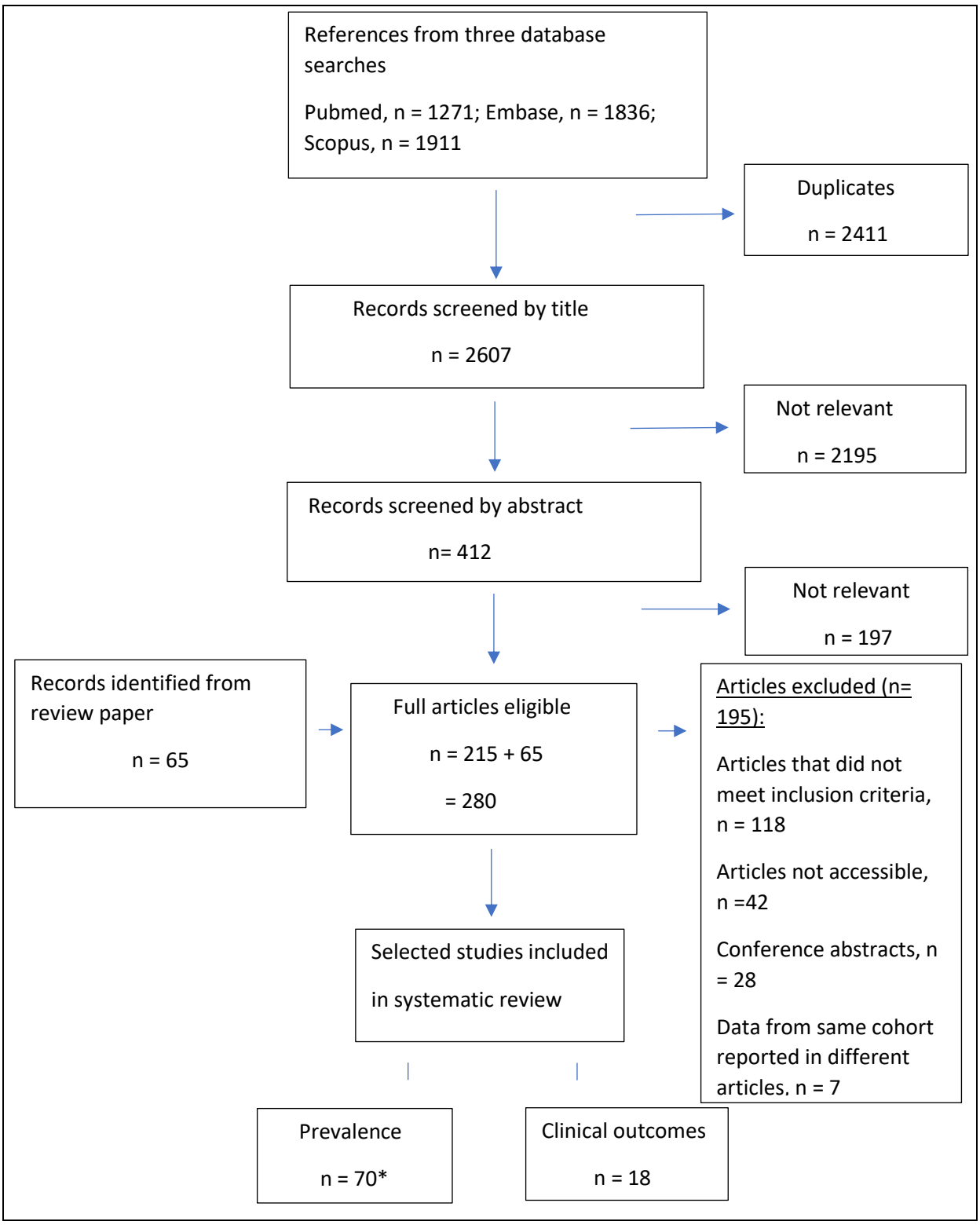


Figure 3.1 Flow diagram of literature search and results of selected studies

*Three studies with clinical outcome data contributed to data on prevalence of TBU in uveitis cases

3.3.3 Prevalence of tubercular uveitis (TBU) in a population of uveitis patients

Among the 70 studies reporting on 65,607 uveitis cases, 3,166 (4.8%) cases were TBU (Table 3.2). The weighted mean age of uveitis cases (means reported in 32 studies) was 39.3 [95% CI, 37.2 – 41.4] years; and 50.0% [95% CI, 48-52] of cases in whom gender was reported were males. The overall weighted prevalence of TBU among uveitis cases was 4.0% [95% CI, 3-5] (Figure 3.2). The pooled weighted prevalence for high-burden countries (HBCs) was 7.0% [95% CI, 5-11] (range: 1.0% to 32.0%) and non-HBCs 3.0% [95% CI, 2-4] (range: < 1.0 to 23.0%) (Figure 3.2); with 'considerable' intergroup heterogeneity (I^2 = 97.92%, p < 0.01). The pooled weighted prevalence for, the High-Income region was 3.0% [95% CI, 2-4], the East Asia, South-East Asia and Oceania region 4.0% [95% CI, 2-8], South Asia region 8.0% [95% CI, 4-14], North Africa and Middle East region 4.0% [95% CI, 2-8], sub-Saharan Africa region 11.0% [95% CI, 8-15], and Latin America and Caribbean region 5.0% [95% CI, 4-6] (Figure 3.3). The pooled weighted prevalence of studies in which, data collection started before 2010 was 3.0% [95% CI, 2-4], and data collection started during or after 2010 was 8.0% [95% CI, 4-12] (Figure 3.4).

The overall weighted prevalence of TBU in the high-quality studies was 6.0% [95% CI, 3-9] (Figure 3.5). The pooled weighted prevalence in high-quality studies for HBCs was 8.0% [95% CI, 2-18] and non-HBCs was 5.0% [95% CI, 3-8]. The pooled weighted prevalence of TBU in studies with no diagnostic criteria; diagnostic criteria that excluded ATT; and diagnostic criteria that included ATT was 2.0% [95% CI, 1-3]; 4.0% [95% CI, 2-6]; and 7.0% [95% CI, 5-10], respectively (Figure 3.6). The weighted prevalence of the 4 studies that mentioned diagnostic criteria proposed by Gupta and coworkers, (Gupta, Gupta and Rao, 2007; Gupta *et al.*, 2015) but did not specify the criteria, was 6.0% [95% CI, 2-12]. The weighted prevalence of TBU varied with study design and was similar at 4.0% [95% CI, 3-5], 5.0% [95% CI, 2-8] and 5.0% [95% CI, 2-9] for case series, cross-sectional and cohort studies, respectively (Figure 3.7).

3.3.4 Clinical outcomes of tubercular uveitis (TBU) patients treated with anti-tubercular medication

The 18 studies reporting clinical outcomes are summarized in Table 3.3. The weighted mean age of TBU patients (means reported in 5 studies) was 39.6 [95% CI: 33.0 – 44.3] years, and 54% [95% CI,48-59] were of male gender (reported in 9 studies). Fifteen of the studies were retrospective, and only 3 prospective cohorts (Table 3.3). Six (33%) of the studies were from TB HBCs (4 from India), and 11 (61%) were from non-HBCs (5 from the United Kingdom) (Table 3.3). One study was multicentred.

The quality of the studies was high and medium in 4 (22%) (Shakarchi, 2015a; Agrawal *et al.*, 2017a; Chung and Li, 2018; Ghauri *et al.*, 2019) and 14 (78%) (Gupta *et al.*, 1998; Babu *et al.*, 2009a; Sanghvi *et al.*, 2011; Ang *et al.*, 2012b; Manousaridis *et al.*, 2013; Balne *et al.*, 2014; Agrawal *et al.*, 2015; Damato *et al.*, 2017; Ng *et al.*, 2017; Ang *et al.*, 2018; Anibarro *et al.*, 2018; Sudheer *et al.*, 2018;

Krassas *et al.*, 2018; Llorenç *et al.*, 2020) studies, respectively (Table 3.3). Cases in 12 studies (Babu *et al.*, 2009a; Sanghvi *et al.*, 2011; Ang *et al.*, 2012b; Manousaridis *et al.*, 2013; Agrawal *et al.*, 2015; Shakarchi, 2015a; Ang *et al.*, 2018; Sudheer *et al.*, 2018; Chung and Li, 2018; Krassas *et al.*, 2018; Ghauri *et al.*, 2019; Llorenç *et al.*, 2020) were treated with 4-drug ATT for the initial 2 months (Table 3.3). In 11 studies (Babu *et al.*, 2009a; Sanghvi *et al.*, 2011; Ang *et al.*, 2012b; Manousaridis *et al.*, 2013; Shakarchi, 2015a; Ang *et al.*, 2018; Sudheer *et al.*, 2018; Chung and Li, 2018; Krassas *et al.*, 2018; Ghauri *et al.*, 2019; Llorenç *et al.*, 2020) this consisted of Rifampicin (R), Isoniazid (H), Pyrazinamide (Z) and Ethambutol (E) for the initial 2 months with Moxifloxacin (M) replacing ethambutol in a few cases in 1 study (Agrawal *et al.*, 2015). The number of ATT drugs was 3 (RHZ) in 1 study (Gupta *et al.*, 1998), not mentioned in 2 studies (Balne *et al.*, 2014; Agrawal *et al.*, 2017a) and varied between cases in 3 studies (Damato *et al.*, 2017; Ng *et al.*, 2017; Anibarro *et al.*, 2018) (Table 3.3). The use of ocular and/or systemic corticosteroids was reported in all the studies. Duration of ATT was 6 months in 7 (39%) studies (Sanghvi *et al.*, 2011; Manousaridis *et al.*, 2013; Balne *et al.*, 2014; Shakarchi, 2015a; Anibarro *et al.*, 2018; Sudheer *et al.*, 2018; Krassas *et al.*, 2018) and ≥ 9 months in 3 (17%) studies (Gupta *et al.*, 1998; Babu *et al.*, 2009a; Ghauri *et al.*, 2019) (Table 3.3). In 7 (39%) studies, there was intra-study variation of ATT duration (Ang *et al.*, 2012b; Agrawal *et al.*, 2015; Damato *et al.*, 2017; Ng *et al.*, 2017; Ang *et al.*, 2018; Chung and Li, 2018; Llorenç *et al.*, 2020). Treatment duration was not mentioned in 1 (5%) study (Agrawal *et al.*, 2017a).

A total of 1,570 TBU cases were treated for TB, of whom 1,304 (83.1%) responded to ATT. The overall weighted clinical (inflammatory) response of TBU cases treated with ATT was 82.0% [95% CI, 75-89] (range: 24.0% to 100.0%) (Figure 3.8). The pooled weighted response to ATT in TB HBCs was 88.0% [95% CI, 83-92] and 79.0% [95% CI, 64-91] in non-HBCs (Figure 3.8). While there was 'considerable' intragroup heterogeneity in the non-HBC group for response to ATT (I^2=92.56%, p<0.01), this was 'not important' in HBC settings (I^2=0.00%, p=0.60). Five studies from HBCs had response to ATT above the weighted mean overall response of 82.0% (Figure 3.8).

The pooled weighted response for studies with duration of ATT ≥ 9 months and 6 months was 83.0% [95% CI, 75-91] and 89.0% [75-98], respectively (Figure 3.9). The pooled weighted response for the studies in which treatment duration varied was 73.0% [95% CI, 55-87]. The pooled weighted response for studies with 3-drug ATT regimen and 4-drug ATT regimen was 90.0% [95% CI, 55-100] and 81.0% [95% CI, 68-91], respectively (Figure 3.10). Studies in which the number of ATT drugs varied between cases had a weighted pooled response of 80.0% [95% CI, 66-92].

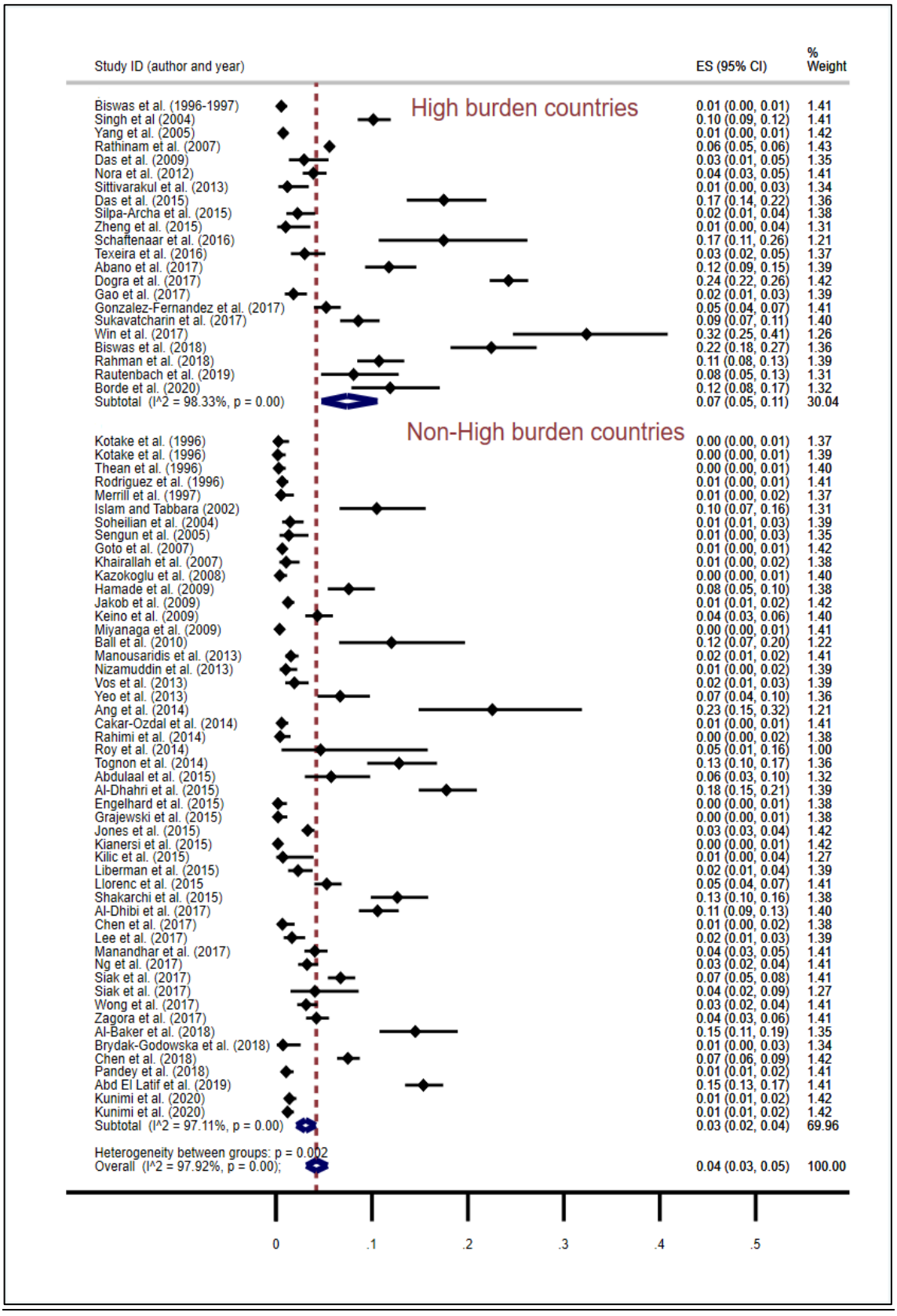


Figure 3.2 Meta-analysis of prevalence studies stratified by high-burden countries (HBCs) and non-high-burden countries (non-HBCs) for TB

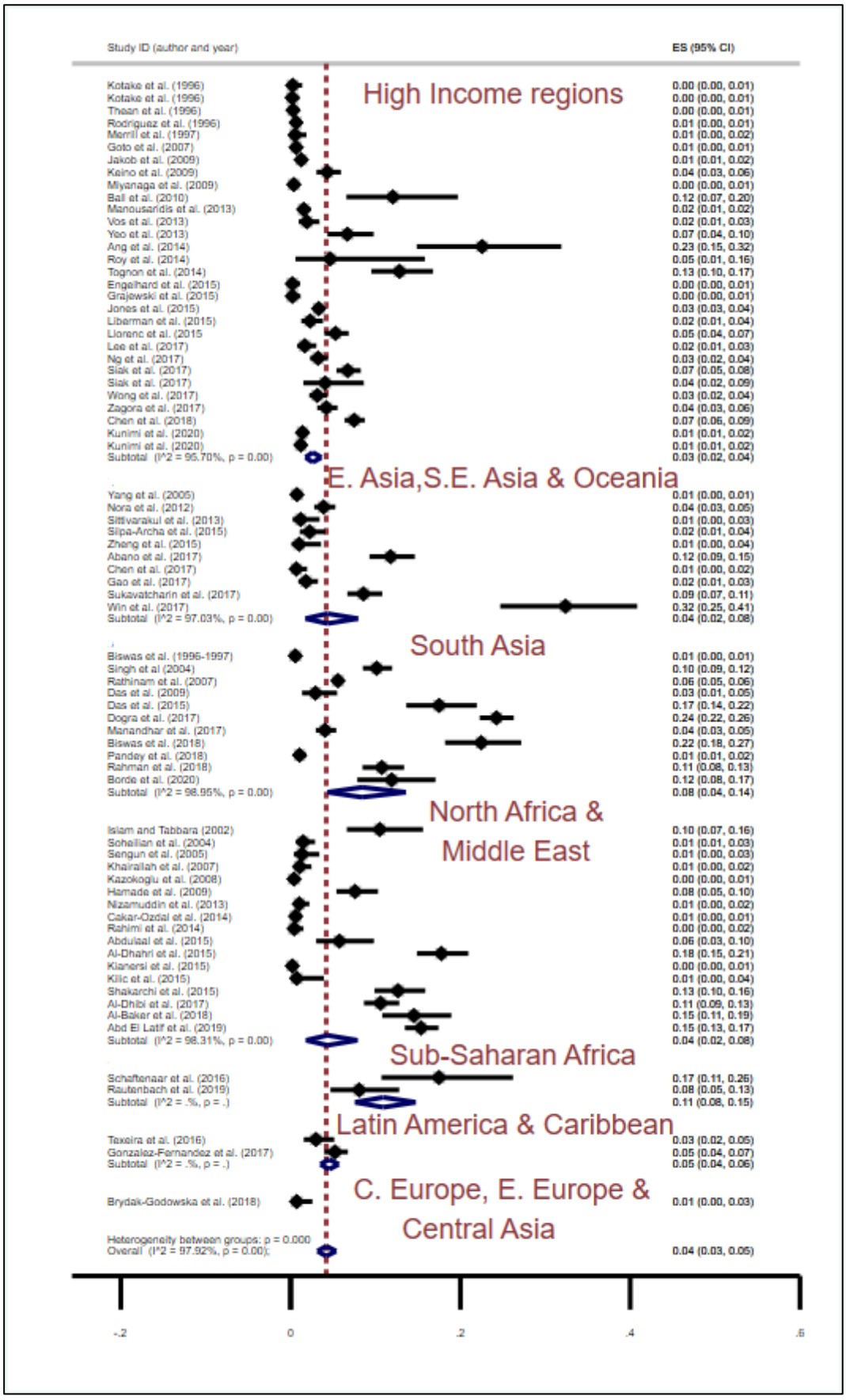


Figure 3.3 Meta-analysis of prevalence studies stratified by seven geographic super-regions defined by the Global Burden of Disease Study (Murray *et al.*, 2012; Vos *et al.*, 2020).

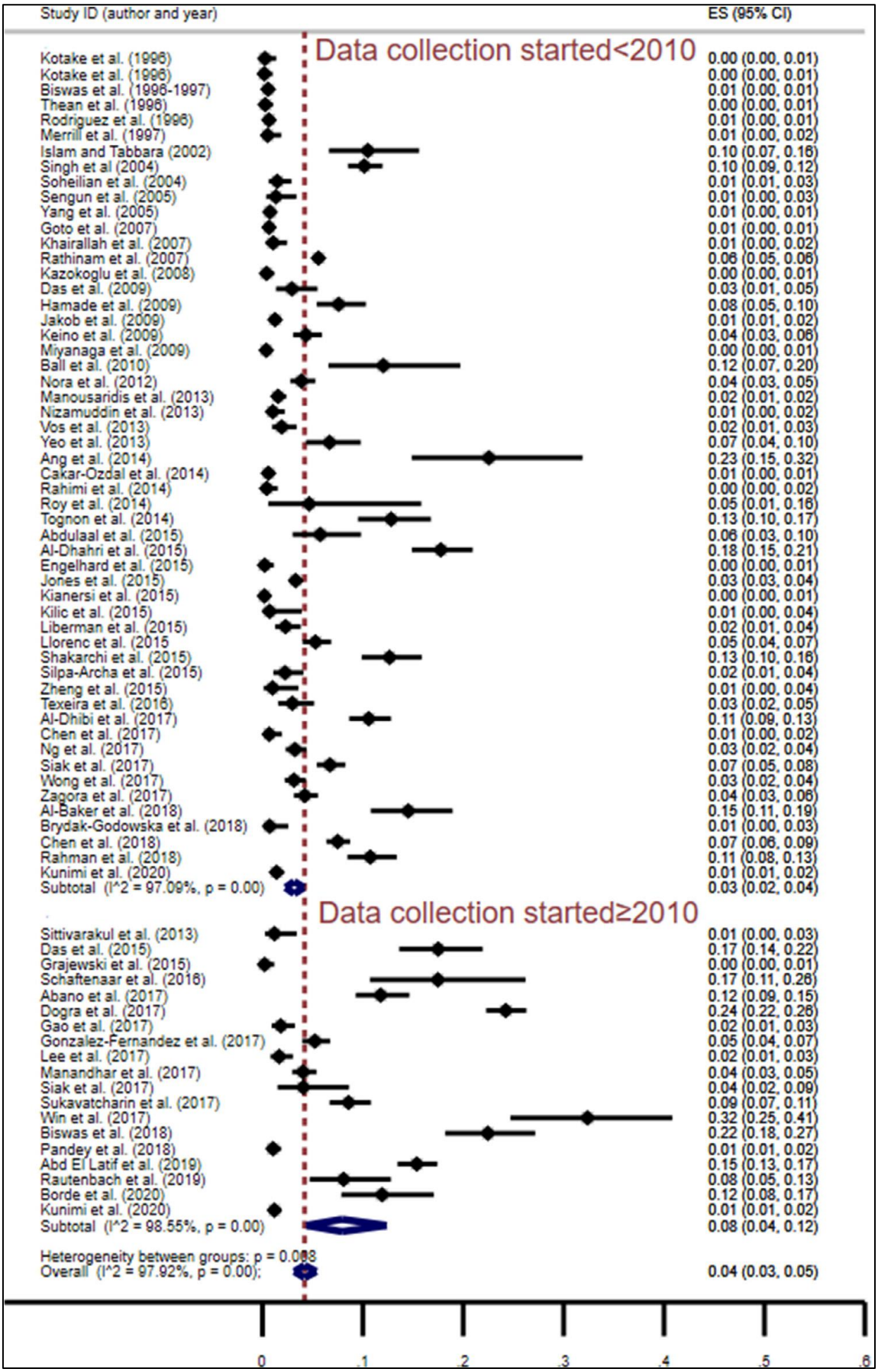


Figure 3.4 Meta-analysis of prevalence studies stratified by data collection started before (<) 2010 and data collection started after and including (≥) 2010

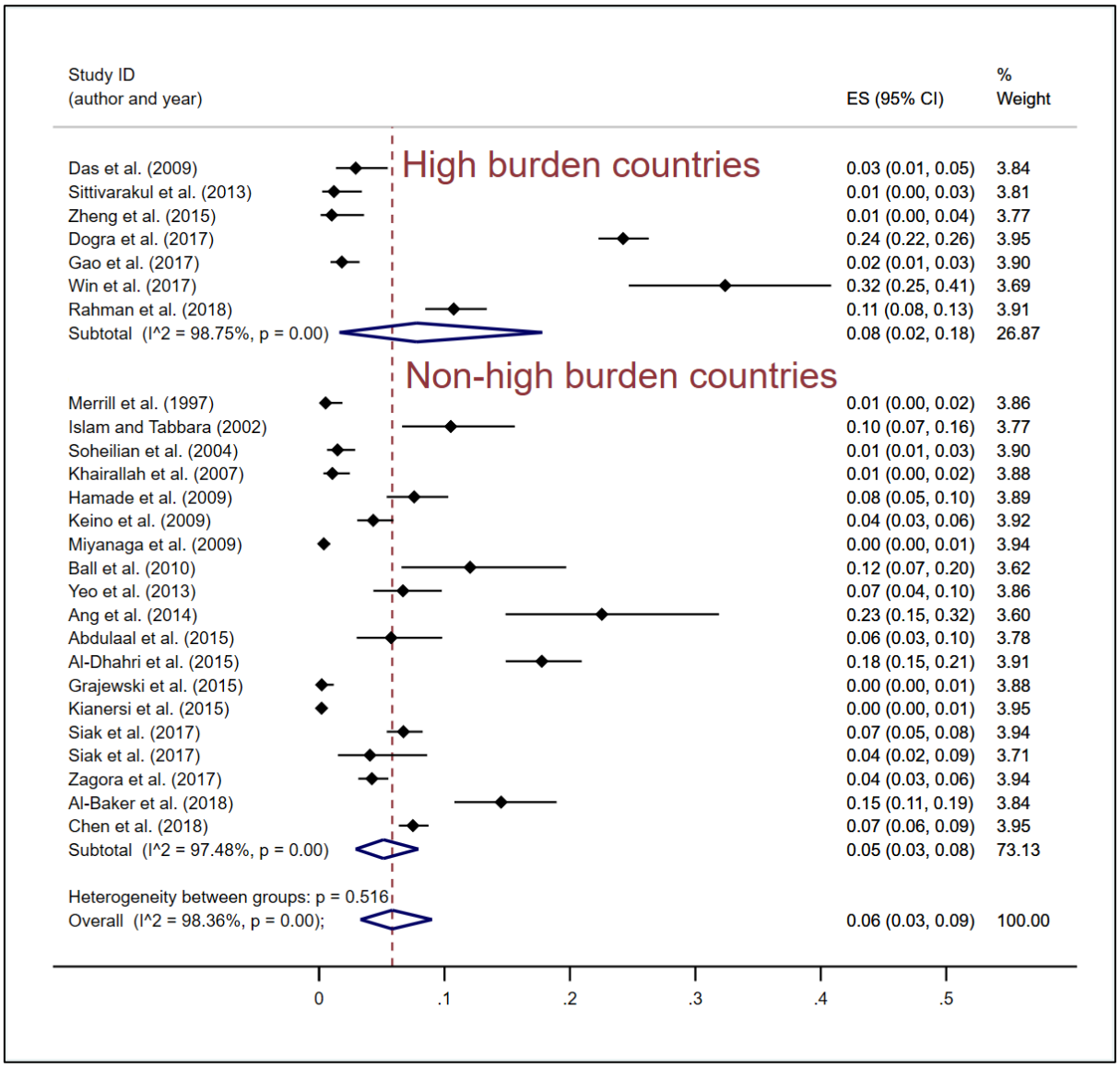


Figure 3.5 Meta-analysis of prevalence of tubercular uveitis of high quality studies

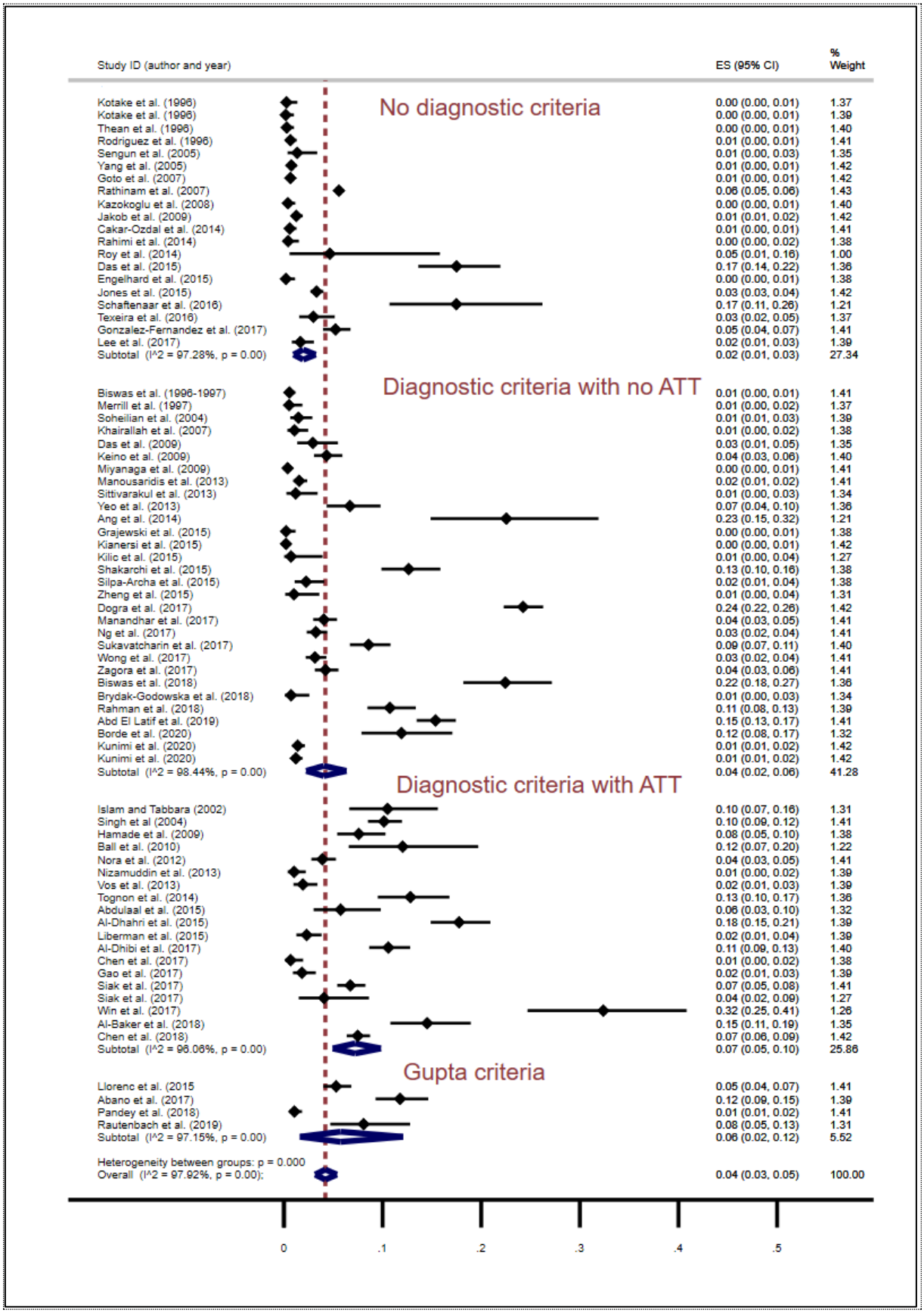


Figure 3.6 Meta-analysis of TB prevalence according to diagnostic criteria

Gupta criteria: Diagnostic criteria according to Gupta et al's. review articles (Gupta, Gupta and Rao, 2007; Gupta *et al.*, 2015) but criteria not specified in the studies.

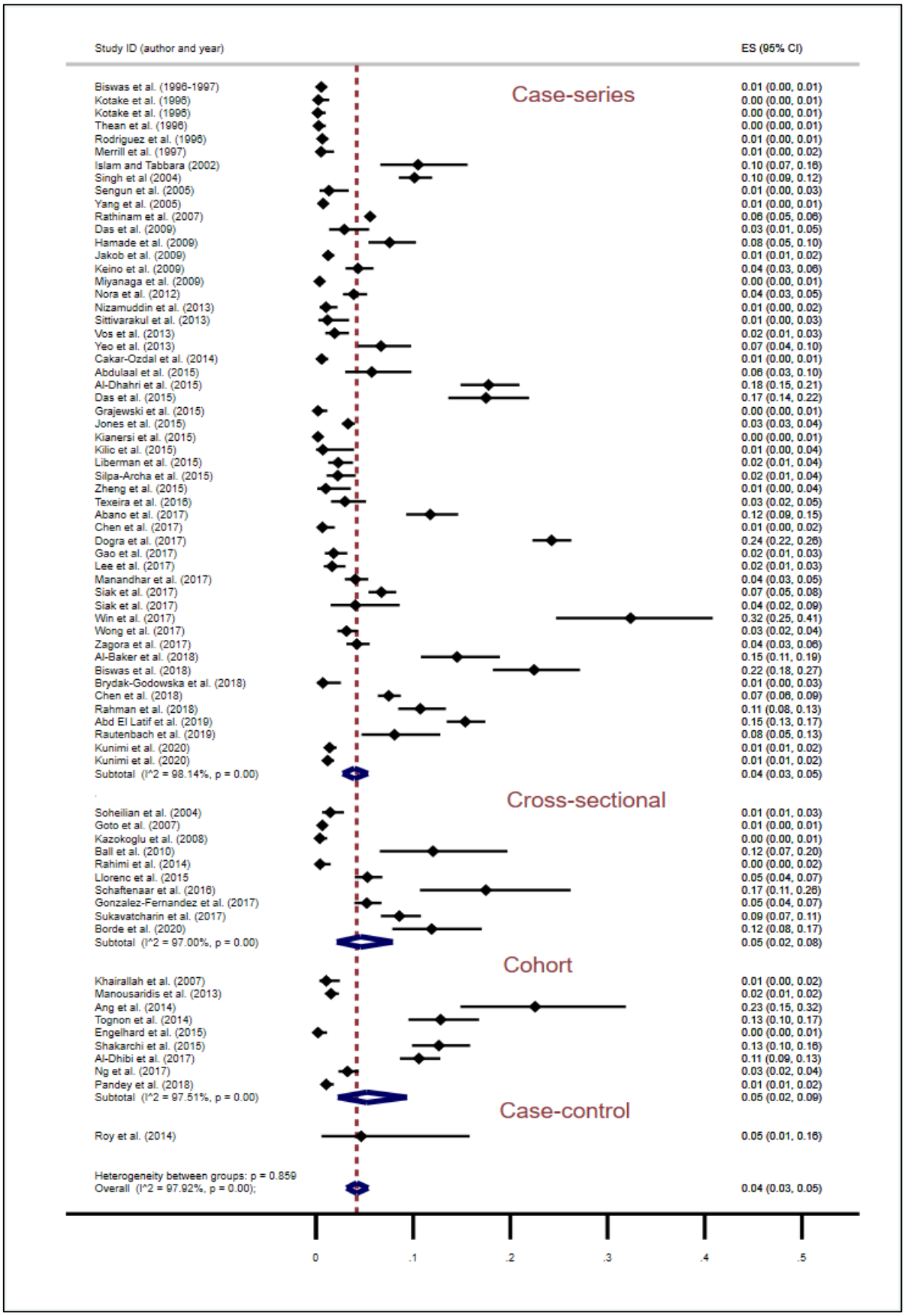


Figure 3.7 Meta-analysis of TB prevalence according to study design

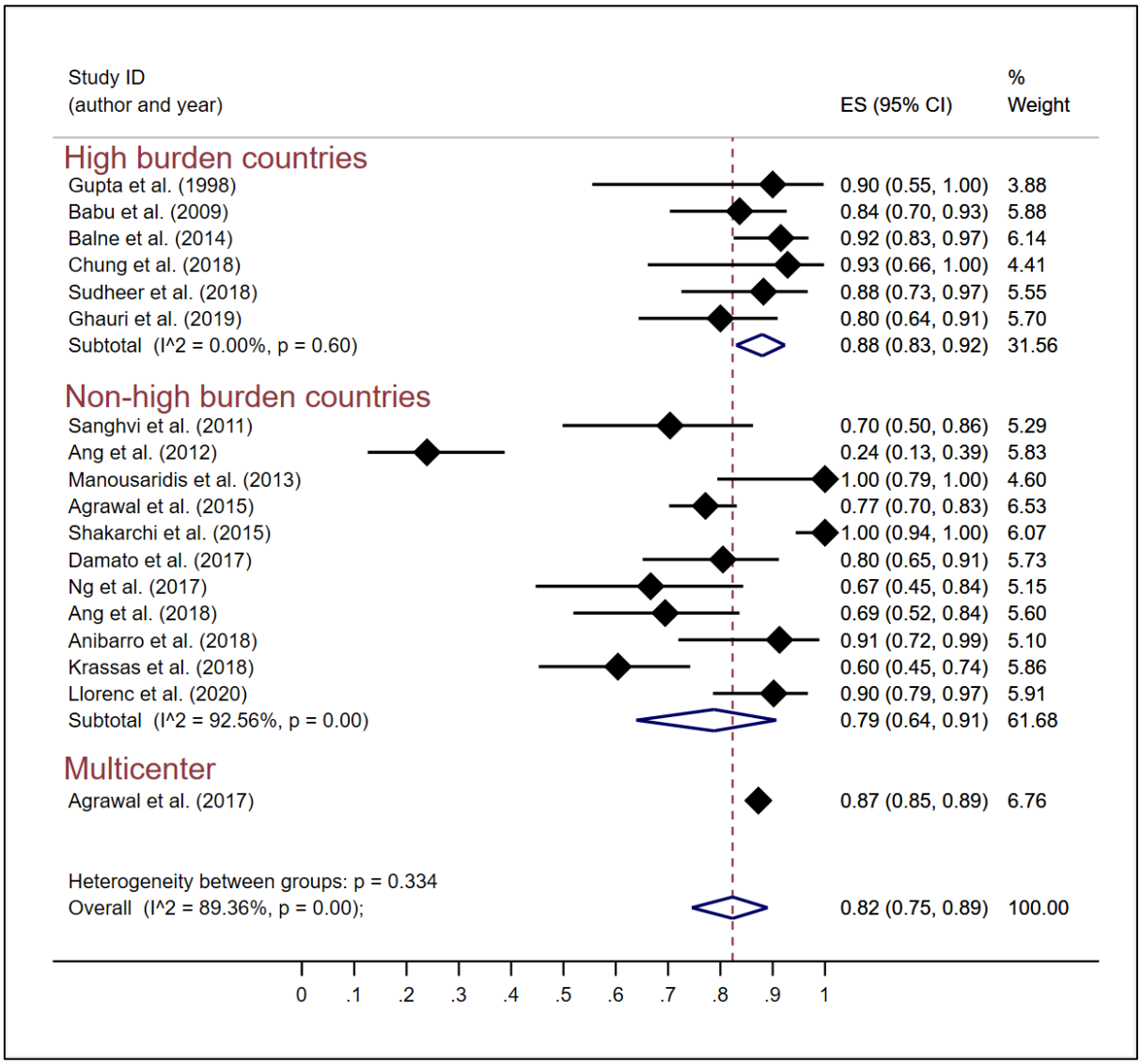


Figure 3.8 Meta-analysis of clinical outcome* studies stratified by high-burden countries (HBCs) and non-high-burden countries (non-HBCs) for TB

* = clinical outcome defined as clinical (inflammatory) response to ATT

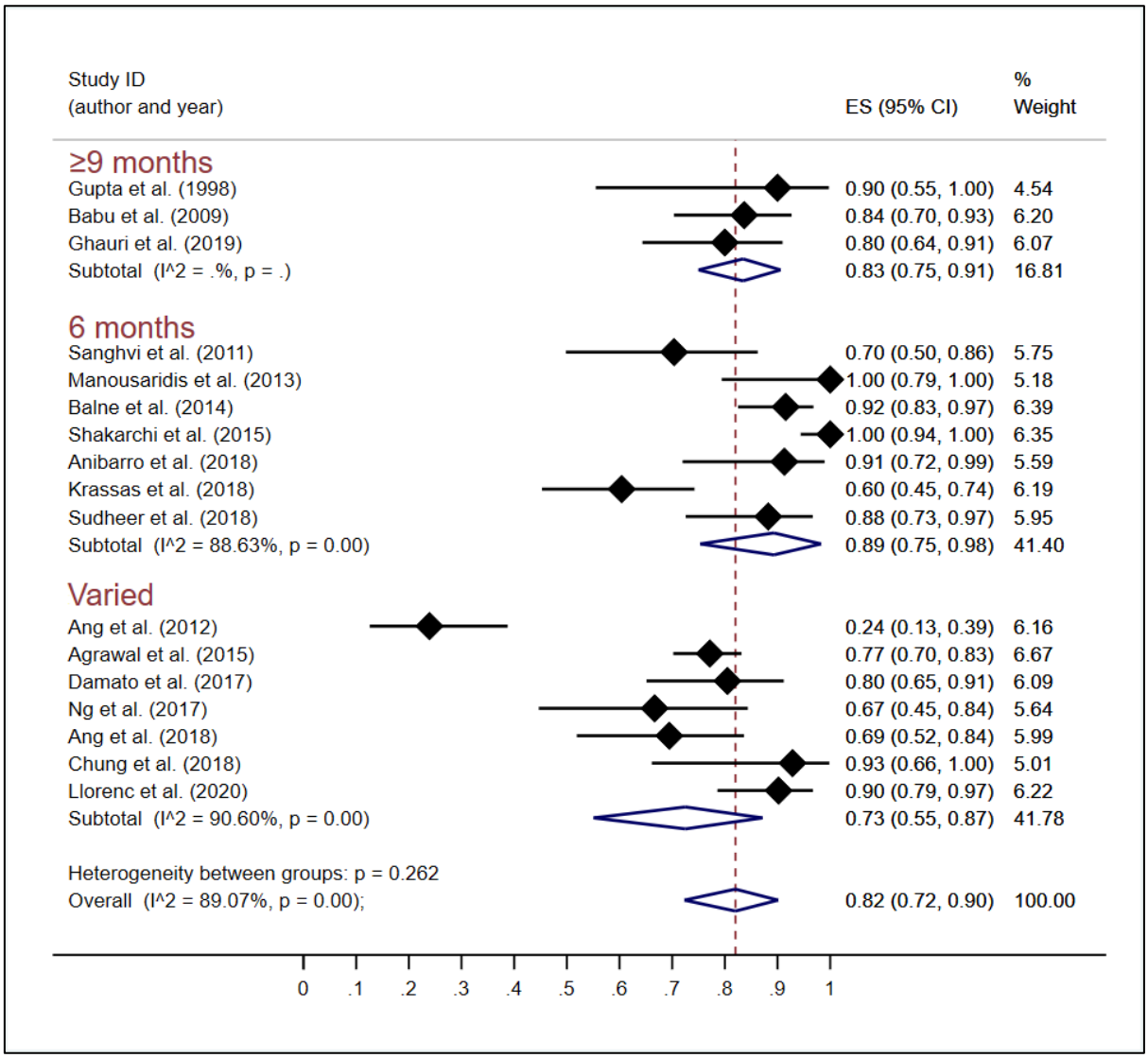


Figure 3.9 Meta-analysis of clinical outcome according to treatment duration

Varied = studies in which ATT duration was < 9 months in some patients and ≥ 9 months in others.

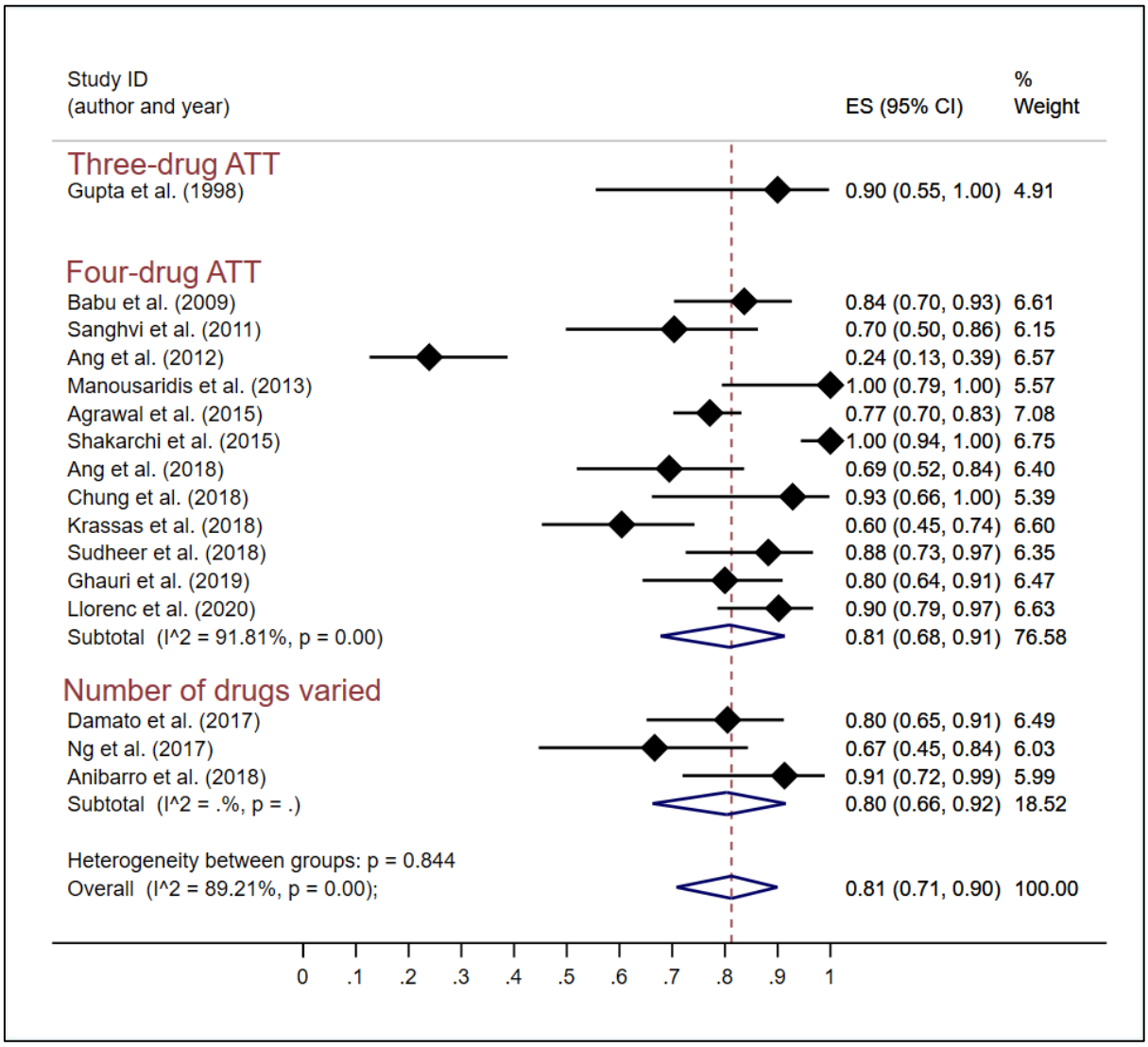


Figure 3.10 Meta-analysis of clinical outcome stratified by the number of anti-tubercular drugs

3.4 Discussion

The global prevalence of TBU in individuals presenting with uveitis was 4.0%, with an expectantly higher pooled prevalence in TB HBCs (7.0%) than non-HBCs (3.0%) (*WHO | Global tuberculosis report, 2019*). To determine a stronger reliable estimate of overall prevalence, we pooled the high-quality studies and observed a prevalence of 6.0%. In terms of the geographic prevalence, sub-Saharan Africa had a significantly higher (11.0%) TBU prevalence than the High-Income region (3.0%) and the Latin America and Caribbean region (3.0%). This is to be expected since sub-Saharan Africa has a higher prevalence of TB than these regions (*WHO | Global tuberculosis report, 2019*). Studies in which data collection started during or after 2010 had a higher TBU prevalence (8.0%) than those in which data collection

started before 2010 (3.0%), albeit it not being significant. This may have been due to widespread application of the combination of diagnostic criteria proposed by Gupta and coworkers from 2010 onward (Gupta, Gupta and Rao, 2007). Overall, there was a considerable level of heterogeneity. This was addressed by separating the studies into HBCs versus non-HBCs for TB, into the different geographic regions, and into studies with data collection before 2010 and during or after 2010. Despite this, the intragroup heterogeneity was still considerable. This may be due to the clinical and methodological diversity in studies within the sub-groups, especially the heterogeneity in the diagnostic criteria for TBU. We attempted to address this by pooling the studies with similar diagnostic criteria, but this did not reduce the level of heterogeneity.

Response to ATT has been suggested as a surrogate for the diagnosis of TBU (Agrawal *et al.*, 2015), and its inclusion in the diagnostic criteria algorithm may assist in improving estimates of the prevalence of TBU in uveitis cases. There may be merit in this statement as studies that included ATT as part of the diagnostic criteria had a significantly higher prevalence (8.0%) than studies with no defined diagnostic criteria (2.0%). There was considerable heterogeneity within the diagnostic criteria groups with ATT and without ATT; this may be due to the heterogeneity in the clinical signs suggestive of TBU and in the diagnostic tests (TST, QFT-G test and microbiological/molecular tests) conducted in the different studies.

Clinical outcome of TBU cases on ATT was measured in terms of resolution or improvement of inflammation after completion of treatment. Studies that reported clinical outcomes only in terms of visual outcomes were not selected because such assessment could be affected by non-inflammatory conditions such as cataracts, macular pathology, glaucoma and optic neuropathy (Durrani, Meads and Murray, 2004).

The clinical outcome in our systematic review and meta-analysis was 82.0%. This estimate is similar to an earlier systematic review published in 2016 (Kee *et al.*, 2016). In addition to ATT, the use of ocular and/or systemic corticosteroids, to control inflammation, was mentioned in all the studies included in our systematic review and meta-analysis. The clinical outcome, stratified by the level of TB burden, showed an 88.0% and 79.0% clinical response for cases from TB HBCs and non-HBCs settings, respectively (Figure 3.8); however, this was not significantly different. The overall heterogeneity for clinical outcomes was considerable. We attempted to address this by pooling the studies into HBCs and non-HBCs for TB, into the different number of ATT drugs, and into the different ATT durations. Despite this, the intra-group heterogeneity was ‘considerable’ in the different sub-groups except for that in HBCs for TB (I^2=0.00%,

p=0.60). The heterogeneity being 'not important' in the HBC group may have been due to the consistent use of oral corticosteroids in addition to ATT in 5 out of the 6 studies.

Although we included studies that had clinical outcomes after the completion of ATT, there were no studies with long-term outcomes. The multicentre Collaborative Ocular Tuberculosis Study (COTS) Group reported a long-term clinical outcome of 77.0% at 24-months (Agarwal *et al.*, 2020) which is slightly lower than the overall response of 82.0% in our meta-analysis. The COTS study group defined 'cure' as TBU-inactivity 24 months after completing ATT. An earlier report of the same cohort, with a clinical response of 87.0%, is included in our meta-analysis (Agrawal *et al.*, 2017a).

The systematic review by Kee and coworkers (Kee *et al.*, 2016) did not report on the treatment outcomes in HBCs and non-HBCs, and did not compare different anti-TB drug regimens, in relation to the number of drugs and duration of treatment. Our analysis of the clinical outcome stratified by the number of drugs showed the pooled clinical outcome for studies with 3-drug (RHZ) ATT in the first 2 months was higher than that for 4-drug (RHZE) ATT (Figure 3.10), but this difference was not significant; however, only 1 study reported on a 3-drug regimen (Figure 8) (Gupta *et al.*, 1998).

In terms of ATT duration, studies that had treatment duration of 6 months compared to ≥9 months had higher clinical outcomes, but this difference was not statistically significant (Figure 3.9). Ang and coworkers and Agrawal and coworkers reported that TBU cases treated with ATT for ≥ 9 months duration had a lower rate of recurrence; whilst inclusion of corticosteroid had no effect on recurrence of inflammation (Ang *et al.*, 2012b; Agrawal *et al.*, 2015) Further studies are needed to elucidate the role of anti-TB drug regimen, especially the duration of treatment, on clinical outcome. The other factors that affect clinical outcome, specifically inflammatory outcome, that need to be considered are: (1) the different corticosteroid regimens used; (2) patient compliance in the different studies, (3) that the TBU might be an immune reaction against tubercular antigens / dormant *Mtb* bacilli and therefore ATT may be less effective in this subgroup of patients (Garip *et al.*, 2009; Wroblewski *et al.*, 2011; Forrester *et al.*, 2013); (4) that a misdiagnosis of TBU is a possibility, given the difficulty in making the diagnosis and; (5) that there might be resistance to ATT (Sharma *et al.*, 2014).

Limitations to this systematic review and meta-analysis include the possibility of eligible articles being missed although we searched 3 different databases. Studies in all languages were

included in the initial search, however, inaccessible published studies in a language other than English, may have been missed.

The stratification of prevalence according to HBCs and non-HBCs is a limitation in that it is not clear-cut; immigrants from TB-high-burden countries may have contributed to the prevalence of TBU in the non-HBC group. Another limitation is the arbitrary division of studies with data collection starting before 2010 and during or after 2010 based on the assumption that the diagnostic criteria defined by Gupta and coworkers would be widespread from 2010 onward (Gupta, Gupta and Rao, 2007).

Limitations in interpreting the data included heterogeneity in the methodology; including lack of standardization in study design, demographic information, diagnostic criteria for TBU (TBU), anti-TB drug regimen, duration of ATT and clinical outcome endpoints. There was also heterogeneity in data quality, the tool of which was adapted from the JBI assessment tool (Munn *et al.*, 2015; Moola S *et al.*, 2017).

The lack of demographic information meant that we were unable to accurately determine the mean age and male to female ratio, and we were unable to stratify prevalence according to age, gender, race, nationality and HIV status. Although comparisons were made across different diagnostic criteria, ATT regimen and treatment duration, there was still heterogeneity in these subgroups. Although we only included articles that had clinical outcomes on completion of ATT, we could not compare clinical outcome across set time frames because of the variation in clinical outcome endpoints.

3.5 Conclusion

Despite the limitations, our systematic review and meta-analysis is the first to estimate the global prevalence of TBU stratified by HBCs and non-HBCs and by different geographic regions. Additionally, it is the first to stratify clinical outcomes by HBCs and non-HBCs. Heterogeneity in the diagnosis and treatment of TBU indicates that future prospective cohort studies with standardized diagnostic criteria and treatment regimens for TBU are warranted.

CHAPTER 4 Tubercular Uveitis in Uveitis Cases in a High HIV Setting: A Prospective Cohort Study

4.1 Introduction

Tuberculosis has varyingly been attributed to causing 0.2% to 32% of uveitis (Kotake *et al.*, 1996; Win *et al.*, 2017). Tubercular uveitis (TBU) can present with clinical features involving different ocular structures (Gupta, Gupta and Rao, 2007), including broad-based posterior synechiae, retinal vasculitis, optic neuropathy, and choroidopathies such as serpiginous-like choroiditis and choroidal granulomas (Babu *et al.*, 2006; Gupta *et al.*, 2010; Ang *et al.*, 2012a; Gupta *et al.*, 2015; Agrawal *et al.*, 2020b). It can result in ocular morbidity such as visual impairment, chronic hypotony, and blindness (Gunasekeran *et al.*, 2018). Adverse visual sequalae following TBU are associated with delay in diagnosis, chronic disease, and posterior uveitis with choroiditis (Gunasekeran *et al.*, 2018). Complications of visual impairment could be due to optic neuropathy, macular oedema, glaucoma, vitreous haemorrhage, cataract, and macular scarring (Gunasekeran *et al.*, 2018).

The diagnostic difficulties of TBU are due to the inherent problems with the diagnostic tests and obtaining the optimal ocular sample for testing. There is a low positive-yield in microbiological or molecular tests of ocular fluids; and low sensitivity and specificity of adjunct immunological tests such as tuberculin skin test (TST) or TB specific interferon gamma release assays such as the QuantiFERON-TB Gold (QFT-G) (Huebner, Schein and Bass, 1993; Arora *et al.*, 1999; Ang, Htoon and Chee, 2009; Sudheer *et al.*, 2018). Consequently, there is no standardized diagnostic criteria for the diagnosis of TBU.

Although Gupta et al proposed the diagnosis of TBU being based on varying combinations of suggestive clinical features of TBU, laboratory investigations, exclusion of other causes of uveitis, and response to anti-tubercular treatment (ATT) (Gupta, Gupta and Rao, 2007; Gupta *et al.*, 2015), a number of studies have based the diagnosis on QFT-G and/or TST and/or polymerase chain reaction (PCR) test in the presence of uveitis (Sanghvi *et al.*, 2011; Manousaridis *et al.*, 2013; Grajewski *et al.*, 2015; La Distia Nora *et al.*, 2018). Studies have reported a higher prevalence (44% to 48%) of TB being associated with uveitis if the diagnosis is based on a positive QFT-G (Gineys *et al.*, 2011; La Distia Nora *et al.*, 2018).

We undertook a prospective cohort study to determine the proportion of TBU cases in adults with uveitis and to examine the associations of ocular clinical features with TBU.

4.2 Materials and methods

We conducted a prospective cohort study of uveitis cases referred to the Uveitis Clinic at St John Eye Hospital between June 2014 and November 2018. St John Eye Hospital is the Ophthalmology Department of Chris Hani Baragwanath Academic Hospital based in Johannesburg, South Africa which has the highest prevalence of human immunodeficiency virus (HIV) infection in the world (*UNAIDS Programme Coordinating Board sees South Africa's AIDS response first-hand*, 2018). It is a public tertiary hospital with limited resources serving a low-income population. The study was approved by the Human Research Ethics Committee (HREC) of the University of the Witwatersrand (M130942) and followed the tenets of the Declaration of Helsinki. Informed consent was obtained from all participants in the study.

Participants were eligible for inclusion in the study if they had any clinical signs of uveitis and were above 18 years of age. If the participant had bilateral uveitis, only one eye (the eye with worse visual acuity and inflammatory activity) was included for PCR testing and statistical analyses. Individuals were excluded if they had: i. previous or concurrent TB infection; ii. traumatic uveitis or post-surgical uveitis; iii. clinically diagnosed uveitis such as acute retinal necrosis (ARN), progressive outer retinal necrosis (PORN), cytomegalovirus (CMV) retinitis, Behcet's disease, Vogt-Koyanagi-Harada (VKH) disease, Fuchs heterochromic iridocyclitis (FHI), sympathetic ophthalmia, birdshot chorioretinopathy, multiple evanescent white dot syndrome (MEWDS), punctate inner choroidopathy (PIC) and acute posterior multifocal placoid pigment epitheliopathy (APMPPE); and iv. uveitis caused by toxoplasmosis, syphilis, systemic lupus erythematosus (SLE) and sarcoid on blood workup and chest radiography.

All individuals presenting to St John Eye Hospital underwent a standard screening protocol for uveitis which included: slit-lamp examination and fundoscopy; and investigations including full blood count and differential, erythrocyte sedimentation rate (ESR), HIV, CD4+ lymphocyte count if HIV-positive, rapid plasma reagin (RPR) and *Treponema pallidum* hemagglutination assay (TPHA), serum angiotensin converting enzyme (sACE) levels, *Toxoplasma* antibodies, antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA) and chest radiograph to exclude other causes of uveitis. Furthermore, we did tuberculin skin testing using the Mantoux method (0.1 ml containing 2TU RT 23 [Statens Serum Institute, Copenhagen, Denmark] injected intradermally) and QuantiFERON-TB Gold (QFT-G [Cellestis Limited, Carnegie, Victoria, Australia]). Also, ocular fluids (aqueous or vitreous samples) were referred to the National TB Reference Laboratory and tested by TB PCR (Xpert MTB/RIF [Cepheid, Sunnyvale, CA], in-house MPB 64 PCR and in-house IS6110 PCR) and a viral panel PCR (varicella-zoster virus [VZV], herpes simplex virus [HSV1 and HSV2], cytomegalovirus

[CMV], Epstein-Barr virus [EBV], and human herpes virus 6 [HHV6]). Optical coherence tomography (OCT), fluorescein angiography (FA) and lumbar puncture were performed depending on the clinical examination and blood results.

The diagnosis of TBU was made using a composite reference which included: i. any clinical signs of uveitis; ii. other causes of uveitis were excluded; and iii. QFT-G, and/or TST, and/or TB PCR of aqueous or vitreous samples were positive. Participants with positive QFT-G and/or TST were diagnosed with presumed TBU and with positive PCR for TB with confirmed TBU. A TST of ≥ 10 mm at 48 hours post intradermal injection, was considered positive in HIV-negative cases; and > 5 mm in HIV-positive cases. A QFT-G ≥ 0.35IU/ml was considered positive as per manufacturer's recommendations. The QFT-G was performed before the TST. Indeterminate QFT-G results were correlated with the TST and the TB-PCR test; if the TST and / or TB-PCR test was positive, the participant was diagnosed with TBU and if these tests were negative, the participant was diagnosed with non-TBU.

All diagnosed TBU cases were treated with ATT for 9 months: Rifafour e-275 (Rifampicin [R] 150 mg, Isoniazid [H] 75 mg, Pyrazinamide [Z] 400 mg, and ethambutol hydrochloride [E] 275 mg) for 1st 2 months, and RIFINAH-150 (Rifampicin 150 mg and Isoniazid 100 mg) or RIFINAH-300 (Rifampicin 300 mg and Isoniazid 150 mg) for 7 months; the dose was weight dependent. If necessary, depending on the severity of inflammation, TBU cases were additionally treated with topical and / or oral corticosteroids. Tubercular uveitis cases were followed up for a further 6 months after completion of ATT, totalling 15 months follow-up. All non-TBU cases were treated with topical steroids and/or systemic corticosteroid and/or immunosuppressive medication and, also followed-up for 15 months. All cases (TBU and non-TBU) were assessed for intraocular inflammation every 6-12 weeks for 15 months. Remission was defined as no inflammatory activity and being on ≤ 10 mg oral prednisone (Jabs *et al.*, 2005) for 6 months duration after completion of 9 months treatment.

Demographic and clinical characteristics were documented in the TBU- and non-TBU-group. Characteristics that were documented and compared included age, gender, HIV status, laterality (unilateral versus bilateral), TB contact, Bacillus Calmette-Guerin (BCG) vaccination at birth, clinical course of uveitis, anatomical classification, type of choroiditis, clinical signs suggestive of TBU (Babu *et al.*, 2006; Gupta *et al.*, 2010; Ang *et al.*, 2012a; Gupta *et al.*, 2015; Agrawal *et al.*, 2020b) and remission of uveitis. Uveitis was anatomically classified as anterior, intermediate, posterior or panuveitis according to the Standardization of Uveitis Nomenclature (SUN) criteria (Jabs *et al.*, 2005). The clinical course of the uveitis (acute, recurrent or chronic) and grading of intraocular inflammation was according to the SUN criteria (Jabs *et al.*, 2005).

The clinical signs suggestive of TBU, from previous studies (Babu *et al.*, 2006; Gupta *et al.*, 2010; Ang *et al.*, 2012a; Gupta *et al.*, 2015; Agrawal *et al.*, 2020b), that were documented and evaluated were broad-based posterior synechiae (PS), vasculitis, optic neuropathy, choroidal granulomas, and serpiginous-like choroiditis. A choroidal granuloma (large) was defined as a solitary mass > 4mm; multifocal choroiditis as multiple discrete lesions (each ≤ 4 mm) or multiple discrete areas of inflammation; and serpiginous-like choroiditis as choroidal lesions that start around the disc and spreading centrifugally which are initially non-contiguous and eventually becoming confluent (Gupta, Gupta and Rao, 2007).[3] Diffuse choroiditis was defined as non-discrete diffuse inflammation of the choroid.

Statistical analysis

Continuous variables were summarized as means (standard deviation) if normally distributed or medians (interquartile range) if they were skewed. The comparison of means between the TBU and non-TBU groups was performed using the two-sample t-test. The comparison of medians between the two groups was performed using the Wilcoxon rank-sum test. A chi-squared or Fisher's exact test was used to compare categorical variables. Univariate logistic regression was used to evaluate the diagnosis of TBU as the outcome with the predictor variables of age, gender, HIV, laterality, TB contacts, BCG at birth, chronicity of uveitis, and clinical signs such as broad-based synechiae, vasculitis, optic neuropathy, serpiginous-like choroiditis, and choroidal granulomas. The selection of variables in the multivariate logistic regression analysis was done by a stepwise regression method using backward elimination, with significance levels ≤ 0.2 for inclusion. The estimate of odds ratio (OR) and its relative 95% confidence interval (CI) were calculated. The models were assessed using receiver operating characteristics (ROC) curves. All analyses were performed using STATA version 16.1 (Statacorp LLC, College Station, Texas). For all tests, $P < 0.05$ was considered statistically significant.

4.3 Results

Forty-nine (62%) of the enrolled 79 cases were diagnosed with TBU, including 41 with presumed TBU and 8 with confirmed TBU (Table 4.1). Of the 30 non-TBU cases, three were positive for VZV on ocular fluid PCR testing. The three cases with VZV infection had no ocular signs suggestive of ARN, PORN and CMV at study entry. Additionally, a further four of the 30 non-TBU cases were positive for EBV on ocular fluid PCR testing. The overall and TBU cases mean (SD) age were 40.1 (12.2) and 41.8 (13.4) years, respectively (Table 4.1). Twenty-

five (32%) of 79 cases were males, albeit there being a lower percentage (18%; 9/49) among the TBU cases. Thirty cases (38%) were living with HIV, including 24% in those with TBU (Table 1). The median (IQR) CD4+ cell count of the HIV-positive cases in the TBU group was 233 (155 – 473) and the non-TBU group 137 (105 – 278). Forty-three (54%), thirty-nine (50%) and eight (10%) cases had a positive TST, QFT-G and TB PCR, respectively (Table 4.2); one case with a positive QFT-G was classified as non-TBU because of a positive VZV PCR test. Forty-nine (62%) cases had at least one positive TB test.

Table 4.1 Baseline characteristics of tubercular uveitis (TBU) and non-tubercular uveitis (non-TBU) cases

	Total	**TBU**	**Non-TBU**	***P*-value**
N (%)	**79 (100%)**	**49 (62%)** [Presumed: 41 (84%) Confirmed: 8 (16%)]	**30 (38%)**	
Age (years) Mean (SD†)	40.1 (12.2)	41.8 (13.4)	37.5 (9.7)	0.135*
Gender Males	25 (32%)	9 (18%)	16 (53%)	**0.001****
HIV‡ (n=78), n (%) Positive	30 (38%)	12 (24%)	18 (62%)	**0.001****
CD4+ cell count/L in HIV‡-positive cases (n=28) Median (IQR)	171 (121–294)	233 (155-473)	137 (105–278)	0.078***
Laterality, n (%)				**0.670****
Unilateral	19 (24%)	11 (22%)	8 (27%)	
Bilateral	60 (76%)	38 (78%)	22 (73%)	

Analyzed eye, n (%)				
Right	37 (47%)	17 (35%)	20 (67%)	
Left	42 (53%)	32 (65%)	10 (33%)	
Anterior chamber/vitreous tap, n (%)				
Anterior chamber	43 (54%)	28 (57%)	15 (50%)	
Vitreous	36 (46%)	21 (43%)	15 (50%)	
TB[§] contact, n (%)	14 (18%)	7 (14%)	7 (23%)	0.307**
BCG[¶] vaccination at birth (n =78), n (%)	66 (85%)	40 (83%)	26 (87%)	0.691**

*Two-sample t-test **Chi^2 test ***Wilcoxon rank-sum test [†]SD = Standard deviation [‡]HIV = Human immunodeficiency virus [§]TB = Tuberculosis [¶]BCG = Bacille Calmette-Guerin

Table 4.2 Clinical characteristics of tubercular uveitis (TBU) and non-tubercular uveitis (non-TBU) cases

	Total	**TBU**	**Non-TBU**	***P*-value**
N (%)	**79 (100%)**	**49 (62%)** [Presumed: 41 (84%) Confirmed: 8 (16%)]	**30 (38%)**	
Anatomical classification, n (%)				
Anterior	1 (1%)	1 (2%)	0 (0%)	
Intermediate	2 (3%)	1 (2%)	1 (3%)	
Posterior	1 (1%)	0 (0%)	1 (3%)	
Panuveitis	75 (95%)	47 (96%)	28 (94%)	0.632*
Course of uveitis (n = 77), n (%)				
Acute	24 (32%)	10 (21%)	14 (48%)	
Chronic	47 (61%)	35 (73%)	12 (42%)	0.006**

Recurrent	6 (7%)	3 (6%)	3 (10%)	
Fundus pathology				
Choroiditis type, n (%)				
Multifocal (multiple lesions, each < 4mm)	52 (66%)	34 (69%)	18 (60%)	0.393**
Serpiginous-like	4 (5%)	4 (8%)	0 (0%)	0.292*
Diffuse	11 (14%)	3 (6%)	8 (27%)	0.010**
Granulomas (≥ 4mm)	7 (9%)	6 (13%)	1 (3%)	0.176**
Vasculitis only	2 (2%)	0 (0%)	2 (7%)	
No fundus lesions	3[♀] (4%)	2 (4%)	1 (3%)	
Clinical signs (Babu *et al.*, 2006; Gupta *et al.*, 2010; Ang *et al.*, 2012a; Gupta *et al.*, 2015; Agrawal *et al.*, 2020b)[†] **suggestive of intraocular tuberculosis**				
Broad-based posterior synechiae	18 (23%)	11 (22%)	7 (23%)	0.928**
Vasculitis	39 (50%)	22 (46%)	17 (57%)	0.352**
Optic neuropathy	4 (5%)	1 (2%)	3 (10%)	0.151*
Choroidal granulomas	7 (12%)	6 (13%)	1 (3%)	0.176**
Serpiginous-like choroiditis	4 (5%)	4 (8%)	0 (0%)	0.292*
Remission for 6 months duration after completing ATT[‡] (TBU, n = 35) or completing anti-inflammatory medication (non-TBU, n = 17), n (%)				**0.073****
Yes	18 (35%)	15 (43%)	3 (18%)	
No	34 (65%)	20 (57%)	14 (82%)	
Tuberculin skin test, n (%)				
Positive	43 (54%)	43 (88%)	0 (0%)	

Quantiferon-TB Gold (n = 78), n (%)				
Positive	39 (50%)	38 (79%)	1[¥] (3%)	
***Mtb* PCR[§] (n = 78), n (%)**				
Negative	67 (86%)	38 (79%)	29 (97%)	
Indeterminate[¶]	3 (4%)	2 (4%)	1 (3%)	
Positive	8 (10%)	8 (17%)	0 (0%)	
Viral PCR[§] (n =78), n (%)				
Varicella zoster virus	3 (4%)	0 (0%)	3 (10%)	
Epstein-Barr virus	5 (6%)	1 (2%)	4 (13%)	
Negative	70 (90%)	47 (98%)	23 (77%)	

*Fishers exact test **Chi^2 test [†]References of studies suggestive of clinical signs of intraocular tuberculosis [‡]ATT = Anti-tubercular treatment [♀] 3 cases had no fundus lesions; one had anterior uveitis and two intermediate uveitis

[¥] One case with a positive QuantiFERON test was classified as non-TBU because of a positive PCR for VZV. [§]PCR = Polymerase chain reaction (*Mtb* = *Mycobacterium tuberculosis* detected by IS6110 and MPB64 [none detected by Gene Xpert]). [¶]Cycle –threshold >35 cycles

Chronicity of uveitis (Table 4.2) was more common in TBU (73%) than non-TBU cases (42%) (*P*= 0.006). Ninety-six percent and 94% of TBU and non-TBU cases had panuveitis (*P*=0.632), respectively (Table 2). Presence of diffuse choroiditis was lower in the TBU (6%) than non-TBU (27%) group (*P*=0.010) (Table 4.2). The prevalence of broad-based PS (*P*=0.928), vasculitis (*P*=0.352) and optic neuropathy (*P*= 0.151) was not significantly different between the two groups. The prevalence of choroidal granulomas (13% vs 3%, *P*=0.176) and serpiginous-like choroiditis (8% vs 0%, *P*=0.292) was higher in the TBU group than the non-TBU group, although the difference was not significant. The proportion of cases in remission for 6 months duration after completing 9 months treatment (Table 4.2) was higher in TBU (43%) than non-TBU groups (18%), albeit it being non-significant (*P*=0.073).

On univariate regression analysis (Table 4.3), the odds of TBU were higher in female cases (OR= 5.08; 95% CI, 1.83 to 14.06 [*P*=0.002]) and cases with chronic uveitis (OR = 4.08; 95% CI, 1.44 to 11.59 [*P*=0.008]), but lower in cases living with HIV (OR = 0.19; 95% CI, 0.07 to 0,54; *P*=0.001). The multivariate logistic regression model was most predictive for the outcome

when the following variables were included in the analysis - gender, HIV, chronic uveitis, and diffuse choroiditis (Chi-squared goodness-of-fit test *P*=0.373; Area under ROC (receiver operating characteristics) curve = 0.803) (Table 4.4 and Figure 4.1). A negative HIV test significantly predicted a diagnosis of TBU on multivariate analysis (OR = 0.313; 95% CI, 0.099 to 0.994; *P*=0.049).

Table 4.3 Univariate logistic regression of variables predicting tubercular uveitis

Variable	**Odds Ratio**	**95% CI**[†]	***P*-value**
Age	1.031	0.990 to 1.074	0.138
Gender (Female)	5.079	1.834 to 14.064	**0.002**
HIV[‡] **Positive**	0.198	0.073 to 0.535	**0.001**
Laterality (Bilateral)	1.256	0.439 to 3.594	0.671
TB contacts	0.548	0.171 to 1.755	0.311
BCG[§] **received at birth**	0.769	0.210 to 2.816	0.692
Course of uveitis			
Acute (reference group)	1.0		
Chronic	4.083	1.438 to 11.590	**0.008**
Recurrent	1.400	0.233 to 8.421	0.713
Choroiditis type			
Multifocal	1.511	0.584 to 3.908	0.394
Serpiginous	1		
Diffuse	0.564	0.351 to 0.906	**0.018**
Choroidal granulomas	4.047	0.463 to 35.396	0.206

Clinical signs (Babu *et al.*, 2006; Gupta *et al.*, 2010; Ang *et al.*, 2012a; Gupta *et al*, 2015; Agrawal *et al.*, 2020b)¶ **suggestive of intraocular tuberculosis**			
Broad-based posterior synechiae	0.951	0.323 to 2.800	0.928
Vasculitis	0.647	0.258 to 1.621	0.353
Optic neuropathy	0.188	0.019 to 1.892	0.156
Choroidal granulomas	4.047	0.463 to 35.396	0.206
Serpiginous-like choroiditis	1		

†CI = Confidence interval ‡HIV = Human immunodeficiency virus §BCG = Bacille Calmette-Guerin
¶References of studies suggestive of clinical signs of intraocular tuberculosis

Table 4.4 Multivariate logistic regression model for variables predicting tubercular uveitis (n=76, Chi-squared goodness-of-fit test *P*=0.373, Area under ROC† curve = 0.803)

Variable	**Odds Ratio**	**95% CI‡**	***P*-value**
HIV§	0.313	0.099 to 0.994	0.049
Gender (Female)	2.831	0.859 to 9.325	0.087
Chronic uveitis	1.483	0.844 to 2.608	0.171
Diffuse choroiditis	0.630	0.372 to 1.067	0.086

†ROC = Receiver operating characteristics ‡CI = Confidence interval
§HIV = Human immunodeficiency virus

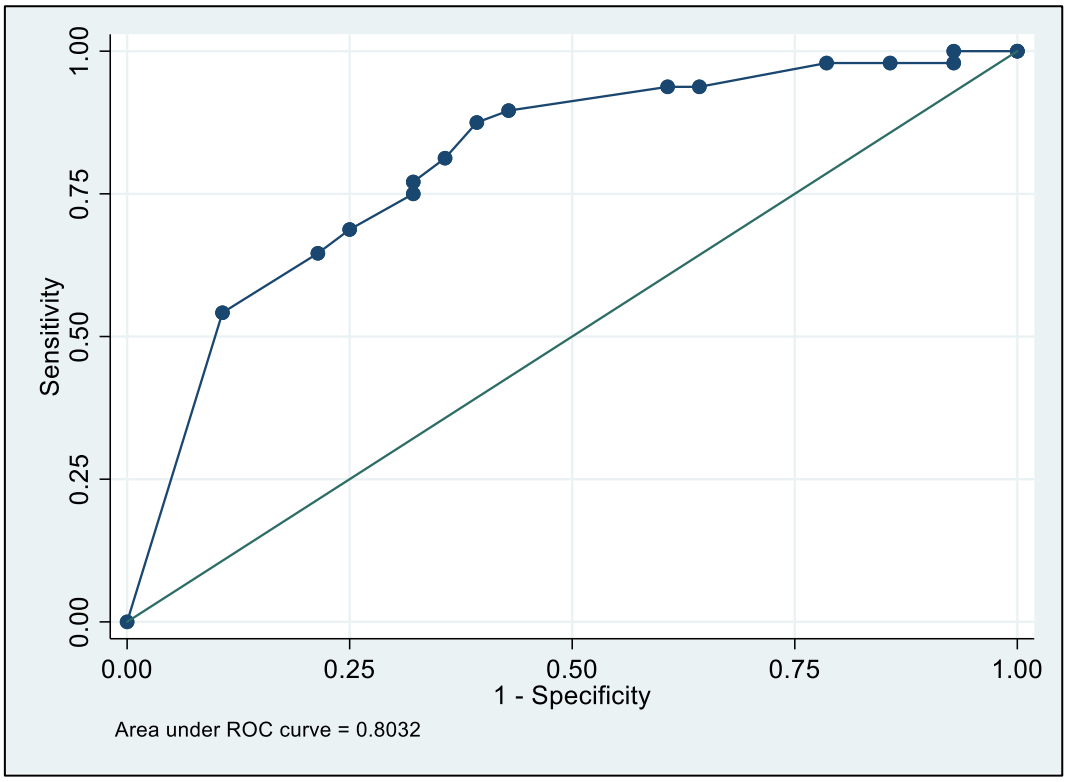


Figure 4.1 ROC (receiver operating characteristics) curve of the multivariate regression model predicting tubercular uveitis

4.4 Discussion

The proportion of TBU cases in our study was 62%. The reported prevalence of TBU in several studies from high TB-burden countries range from 22-48% (Schaftenaar *et al.*, 2016; Dogra *et al.*, 2017; Win *et al.*, 2017; Smit, Esterhuizen and Meyer, 2018; Biswas, Kharel Sitaula and Multani, 2018; La Distia Nora *et al.*, 2018) and from non-high TB-burden countries range from 7-44% (Gineys *et al.*, 2011; Yeo *et al.*, 2013). Although we report a higher proportion of TBU cases, direct comparison of our data to these studies is not possible because the prevalence of TBU reported in these studies is in a uveitis population that included cases with other aetiologies. Our study excluded uveitis cases that had a specific aetiology, such as ARN, PORN, CMV retinitis, Behcet's disease, VKH, FHI, sympathetic ophthalmia, birdshot chorioretinopathy, MEWDS, APMPPE, PIC toxoplasmosis, syphilis, SLE, and sarcoid. The other reason for the high proportion of TBU cases in our study is that the diagnosis of TBU was based on a composite reference, including any of the following three positive tests – QFT-G, TST, and/or PCR. If a single test alone were used to make the diagnosis, the prevalence would have been lower. For example, the QFT-G-positivity rate in our study was 50%. In high TB-

burden countries the QFT-G-positivity rate in all uveitis cases is reported at between 36% - 48% (La Distia Nora *et al.*, 2018; Pathanapitoon *et al.*, 2018). Gineys et al., from a low TB-burden country, reported a QFT-G positivity of 44% and proposed the treatment of TBU based on a positive QFT-G and TST (Gineys *et al.*, 2011). As mentioned above, the higher proportion of TBU patients may be due to an overestimation of the prevalence of TBU. Alternatively, it may reflect an accurately high proportion of TBU as evidenced by the higher proportion of TBU cases in remission for the duration of 6 months after completing ATT compared to non-TBU cases (43% vs 18%). The difference was, however, not significant and a larger sample size may have shown significance between the two groups.

There was a significantly higher proportion of females and HIV-negative cases in the TBU-group. These findings were similar to the study by Smit et al., which was also conducted in South Africa (Smit, Esterhuizen and Meyer, 2018). Although several studies (Cailhol, Decludt and Didier, 2005; Sreeramareddy *et al.*, 2008; Peto *et al.*, 2009) have shown that females were strongly associated with extra-pulmonary TB (EPTB), some studies (Sanghvi *et al.*, 2011; Manandhar, 2017; Smit, Esterhuizen and Meyer, 2018) on TBU showed a female preponderance while others (Manousaridis *et al.*, 2013; Agrawal *et al.*, 2017a) (including the Collaborative Ocular Tuberculosis Study (COTS)-1) did not. This gender effect in EPTB is thought to be related to access to healthcare, socio-economic factors, and hormonal factors (Cailhol, Decludt and Didier, 2005; Sreeramareddy *et al.*, 2008). Although on univariate analysis female gender was significantly associated with TBU, this significance was lost in the multivariate analysis. There was a significantly higher proportion of HIV negative cases in the TBU group. Since the diagnosis of TBU in most cases was based on a positive QFT-G or TST, a lower proportion of TBU cases being HIV-positive may be due to higher false negative TB tests secondary to immunosuppression. This is supported by the lower median CD4+ cell count in the non-TBU group. Because the sensitivity of these immunological tests is reduced in immunosuppressed individuals (Huebner, Schein and Bass, 1993; Leidl *et al.*, 2010), the diagnosis of TBU could have been underestimated in the HIV-positive cases. The T-spot.TB® (Oxford Immunotech, UK) test is more sensitive in diagnosing TB in HIV-positive individuals with lower CD4+ cell counts (Bocchino *et al.*, 2009) and might have yielded more TBU cases in our study; however, it is not available at our hospital. A study from Cape Town in South Africa also found a higher proportion of HIV negative cases diagnosed with possible intra-ocular TB (Smit, Esterhuizen and Meyer, 2018) the QFT-G test was used to support the diagnosis. In our study, a negative HIV test was significantly associated with TBU on both univariate and multivariate analyses.

The most common anatomic diagnosis in the TBU- and non-TBU groups was panuveitis. The high prevalence of panuveitis reflects the referral pattern in our hospital; most anterior and intermediate uveitis are treated in the outpatient area and rarely referred to our uveitis clinic. Tubercular uveitis predominantly manifested as panuveitis in several studies (Al-Mezaine, Kangave and Abu El-Asrar, 2010; Gineys *et al.*, 2011; Sanghvi *et al.*, 2011). In the COTS study the most common anatomic presentation was posterior uveitis followed by panuveitis (Agrawal *et al.*, 2017a). There was a significantly higher proportion of cases with chronic uveitis in the TBU group compared to the non-TBU group. If there was selection bias in that only chronic cases who did not respond to immunosuppressive treatment, were referred, then this would have been reflected in both the TBU- and non-TBU groups. Chronic uveitis was significantly associated with TBU on univariate analysis, but not on multivariate analysis.

Choroidal granulomas and serpiginous-like choroiditis are commonly associated with TBU (Gupta *et al.*, 2010; Bansal *et al.*, 2012; Agrawal *et al.*, 2020b). In our study there was a higher proportion of cases with choroidal granulomas and serpiginous-like choroiditis in the TBU group than in the non-TBU group; however the difference was not significant and this may possibly be due to the small sample of cases with these signs. Diffuse choroiditis was significantly associated with non-TBU on univariate analysis, but not on multivariate analysis.

Broad-based posterior synechiae, retinal vasculitis and optic neuropathy are signs reportedly associated with TBU (Gupta *et al.*, 2010; Gupta *et al.*, 2015). In our study, there was no significant difference of these signs between the TBU-group and the non-TBU group. The reason for this may be due to the small number of cases with these clinical signs.

Limitations of our study include the limited number of cases in the subgroups, selection bias and as with all studies on TBU, the lack of a gold standard for the diagnosis of TBU. The limited number of cases in the clinical subgroups meant that, although differences in clinical signs were found between the TBU and non-TBU groups, statistical significance may not have been reached because of this. Selection bias may have contributed to the high proportion of TBU and the high proportion of panuveitis. The exclusion of uveitis cases with other aetiologies probably resulted in a higher proportion of TBU, and the possible frequent referral of cases with panuveitis may have resulted in a higher proportion of these cases. The lack of a gold standard for the diagnosis of TBU and the reliance mainly on QFT-G and/or TST for its diagnosis may have contributed to the high proportion of TBU cases. Also, the lack of a gold standard makes the determination of the predictors difficult. But it is because of this diagnostic difficulty we were looking for clinical predictors for the diagnosis of TBU. Strengths of the study include it

being a prospective cohort study with a comprehensive ophthalmic and investigative evaluation, including QFT-G, TST and TB PCR.

In conclusion, because of the inherent problems in the diagnostic tests for TBU, including in cases living with HIV, the true prevalence of TBU is difficult to determine. However, based on the higher remissions achieved in the TBU cases, we found these tests, especially QFT-G and TST, to be useful in the diagnosis of TBU. Tubercular uveitis was associated with a chronic course and HIV-negative cases. In terms of the other clinical predictors of TBU, we could not significantly confirm the clinical features associated with TBU reported in other studies because of the limited number of cases in the clinical subgroups. Thus, there is a need for a large multicenter prospective cohort study to determine the clinical predictors of TBU.

CHAPTER 5 Treatment Outcome of Tubercular Uveitis in a High TB and HIV Setting: A Prospective Cohort Study

5.1 Introduction

Tubercular uveitis (TBU) is defined as intraocular inflammation secondary to *Mycobacterium tuberculosis* infection (Agrawal *et al.*, 2019). There is no gold standard for its diagnosis, and therefore the diagnosis of TBU is challenging (Gupta, Gupta and Rao, 2007). Tubercular uveitis is defined as definite if the microbiological / molecular tests of intraocular fluid are positive. However, the poor positivity rate (37.7% - 58.8%) of these tests has resulted in the diagnosis of TBU in most cases being mainly presumptive (Gupta *et al.*, 1998; Arora *et al.*, 1999; Sudheer *et al.*, 2018). A diagnosis of presumed TBU, following exclusion of other causes of uveitis, is often based on a combination of clinical signs of uveitis, tuberculin skin test (TST) or interferon-gamma release assay (IGRA) reactivity, chest radiography and / or non-ocular microbiological / molecular tests, and / or a positive response to anti-tubercular treatment (ATT) (Gupta, Gupta and Rao, 2007; Gupta *et al.*, 2016).

Treatment outcomes of TBU vary; this is partly due to the misdiagnosis of TBU, resistance to ATT, variation in ATT regimen (including treatment duration), and the variation in the concomitant corticosteroid-use to control inflammation (Alli *et al.*, 2021). Good recovery rates on ATT with corticosteroids have been reported in individuals with presumed (93-100%) (Manousaridis *et al.*, 2013; Shakarchi, 2015a; Chung and Li, 2018) and definite (90%-92%) (Gupta *et al.*, 1998; Balne *et al.*, 2014) TBU. However, lower recovery rates (24% to 67%) in presumed TBU cases have been reported (Ang *et al.*, 2012b; Ng *et al.*, 2017; Krassas *et al.*, 2018). The Collaborative Ocular Tuberculosis Study (COTS) reported a recovery rate of 87.0% in presumed TBU cases 6 months after completing ATT (Agrawal *et al.*, 2017b). A follow-up of the same cohort of cases yielded a long-term recovery rate of 77.0% at 2 years (Agarwal *et al.*, 2020). A meta-analysis of treatment outcomes reported an overall global recovery rate of 82% in TBU cases after completing ATT (Alli *et al.*, 2021).

The optimal duration of ATT yielding a good treatment response with minimal risk of adverse events has been debated. Alvarez et al. and Vos et al. mentioned that treatment for presumed TBU should be stopped in cases responding poorly after 2 – 4 months of ATT (Alvarez, Roth and Hodge, 2009; Vos *et al.*, 2013). However, this may be too early to consider terminating treatment as other studies have reported poor treatment outcomes in cases treated for a shorter duration (Ang *et al.*, 2012b; Agrawal *et al.*, 2015). Cases receiving ATT and concomitant corticosteroids for 3 months had a lower recovery rate (50%) than cases treated for 9 months or

longer (77%) (Agrawal *et al.*, 2015). A longitudinal study assessing recurrence rates in TBU cases treated with concomitant ATT and corticosteroids for at least 12 months reported a low recurrence rate (16%) (Bansal *et al.*, 2008). Another longitudinal study reported a recurrence rate of 30% in TBU cases treated with a similar regimen for 6 months (Tomkins-Netzer *et al.*, 2018).

Although studies seem to suggest that a shorter ATT duration for TBU is inadequate for a good outcome, longitudinal studies assessing the minimum treatment duration needed to achieve significant resolution are sparse. We, therefore, performed a prospective cohort study to determine the timeframe when significant resolution of inflammation in TBU cases on standard ATT for 9 months occurs, and the duration of time resolution is maintained. Additionally, we sub-analyzed the timeframe to resolution according to HIV status.

5.2 Materials and methods

We undertook a prospective, descriptive cohort study of individuals referred to the uveitis clinic at St John Eye Hospital from 2014 until 2018. St John Eye Hospital is a tertiary hospital in Johannesburg, South Africa, a country which is endemic for TB and which has the highest prevalence of human immunodeficiency virus (HIV) infection in the world (*UNAIDS Programme Coordinating Board sees South Africa's AIDS response first-hand*, 2018; *WHO | Global tuberculosis report, 2019*). Individuals were included in the study if they, i. had active uveitis, ii. were ≥ 18 years of age, iii. had no prior or concurrent pulmonary or other extrapulmonary TB, and iv. had no previous ATT. Excluded from the study were individuals that had: i. traumatic uveitis or post-surgical uveitis; ii. clinically diagnosed uveitis such as acute retinal necrosis (ARN), progressive outer retinal necrosis (PORN), cytomegalovirus (CMV) retinitis, Behcet's disease, Vogt-Koyanagi-Harada (VKH) disease, Fuchs heterochromic iridocyclitis (FHI), sympathetic ophthalmia, HLA-B27-associated acute anterior uveitis (AAU), birdshot chorioretinopathy, multiple evanescent white dot syndrome (MEWDS), punctate inner choroidopathy (PIC) and acute posterior multifocal placoid pigment epitheliopathy (APMPPE); and iii. uveitis caused by toxoplasmosis, syphilis, systemic lupus erythematosus (SLE) and sarcoid on blood workup and chest radiography. Uveitis was defined as 'presumed idiopathic' in participants included in the study, if no cause was found on clinical examination, blood workup and chest radiography.

The investigative work-up to exclude other causes of uveitis before study entry were 1. chest radiograph; and 2. laboratory evaluation, such as full blood count (FBC) and differential, erythrocyte sedimentation rate (ESR), human immunodeficiency virus (HIV) ELISA, CD4+

lymphocyte count if HIV-positive, rapid plasma reagin (RPR) and *Treponema pallidum* hemagglutination assay (TPHA), serum angiotensin converting enzyme (sACE) levels, *Toxoplasma* antibodies, antinuclear antibodies (ANA) and antineutrophil cytoplasmic antibodies (ANCA). We performed an ophthalmological assessment and investigative evaluation on all included participants which included, 1. anterior and posterior segment examination; 2. Tuberculin skin test (Mantoux method [Statens Serum Institute, Copenhagen, Denmark])), QuantiFERON-TB Gold test (QFT-G [Cellestis Limited, Carnegie, Victoria, Australia]), and anterior chamber or vitreous tap which was sent for PCR to identify MTB (Xpert MTB/RIF [Cepheid, Sunnyvale, CA], in-house MPB 64 PCR and in-house IS6110 PCR). Participants presenting with bilateral uveitis had ocular fluid from one eye (the eye with the worse visual acuity and inflammatory activity) sampled for PCR testing. Based on the results of the investigative evaluation, TBU cases were identified from the cohort of presumed idiopathic uveitis cases.

We diagnosed TBU as follows: i. Confirmed or definite TBU if TB PCR was positive and possible or presumed TBU if TST and/or QFT-G were positive in the presence of uveitis; and ii. All other causes of uveitis were excluded. A TST ≥ 10 mm induration 48 hours after intradermal injection in HIV-negative patients was considered positive for TBU, and in HIV-positive patients ≥ 5mm (*Fact Sheets | Testing & Diagnosis | Fact Sheet - Tuberculin Skin Testing | TB | CDC*, 2020). The TB antigen value minus the negative control value ≥ 0.35 IU/ml in the QFT-G test was considered positive for TBU. The TST was performed after the QFT test. The IS6110 and MPB64 gene sequence of *Mycobacterium tuberculosis* were the targets used for PCR.

All cases diagnosed with TBU were treated with fixed dose combination ATT. Rifafour e-275 (Rifampicin [R] 150 mg, Isoniazid [H] 75 mg, Pyrazinamide [Z] 400 mg, and ethambutol hydrochloride [E] 275 mg) was prescribed for the first 2 months, and RIFINAH-150 (Rifampicin 150 mg and Isoniazid 100 mg) or RIFINAH-300 (Rifampicin 300 mg and Isoniazid 150 mg) for the remaining 7 months. The total duration of ATT was 9 months, and the dose was weight dependent. To control the inflammatory activity, TBU cases were additionally treated with corticosteroids during and after completion of ATT. Topical corticosteroids were prescribed for TBU cases with anterior uveitis; oral and / or periocular corticosteroids for intermediate and posterior uveitis; and oral and / or topical and / or periocular corticosteroids for panuveitis. Periocular steroids were mainly advocated for cystoid macular oedema. Tubercular uveitis cases were followed up for a further 6 months after completion of ATT, totaling 15 months follow-up.

We assessed all TBU cases for intraocular inflammation at 1.5-, 3-, 6-, 9-, 12- and 15-months post-diagnosis. At each follow-up visit the grading and outcome of intraocular inflammation was according to the standardization of uveitis (SUN) criteria (Jabs *et al.*, 2005). Resolution, which was the outcome measured during the study, was defined as no intraocular inflammation on ≤ 10 mg oral prednisone (Jabs *et al.*, 2005). Remission was defined as no inflammatory activity and being on ≤ 10 mg oral prednisone for 6 months duration after completion of 9 months ATT (Jabs *et al.*, 2005). Participants that had bilateral uveitis were regarded as having achieved resolution or remission when they had no intraocular inflammation in both eyes.

The study was approved by the Human Research Ethics Committee (HREC) of the University of the Witwatersrand (M130942) and followed the tenets of the Declaration of Helsinki. Informed consent was obtained from all included participants prior to study entry.

Statistical analysis

All data were collected and managed using the REDCap (Research Electronic Data Capture) tools hosted at the University of the Witwatersrand (Harris *et al.*, 2009, 2019). Data was analyzed in Stata 16.1 (Statacorp, College Station, Texas). Continuous variables were summarized as means (standard deviations) if they were normally distributed and medians (interquartile range) if they were skewed. Missing data for the longitudinal analysis of resolution was addressed using multiple imputation with chained equations as the pattern of missingness was non-monotone. For the longitudinal analysis of resolution as the outcome across all visits we used a two-level multilevel mixed effects model as well as generalized estimating equations, the former to evaluate the individual level response and the latter to evaluate the population level response. An alpha-level of 0.05 was taken to be statistically significant.

5.3 Results

Seventy-nine presumed idiopathic uveitis cases were enrolled in the study; 49 (62%) were diagnosed with TBU of whom 41 (52%) cases were presumed TBU and 8 (10%) confirmed TBU (Table 1). The mean (SD) age of the TBU cases at diagnosis was 41.8 (13.4) years. Cases with TBU were more likely to be female (82%) and HIV-negative (76%), and to have chronic uveitis (73%) (Table 5.1). Ninety-six percent of the TBU anatomical classification type was panuveitis and 69% of cases had multifocal choroiditis (Table 5.1). Of the 49 TBU cases treated with anti-tubercular medication, concomitant oral corticosteroids were initiated in 46 (94%) cases, of which 43 cases were additionally treated with topical corticosteroids and six cases with periocular corticosteroids; one TBU case was treated with topical corticosteroids only

(Table 5.1). Two TBU cases had no concomitant corticosteroid treatment. Thirty-five TBU cases (71%) completed study follow-up through to 15-months post-diagnosis, of whom 15 (43%) were in remission (Table 5.1).

Table 5.1 Baseline and clinical characteristics, and treatment outcomes of tubercular uveitis (TBU) cases

	TBU[a]
N (%)	49 (62%)
Age (years) Mean (SD)	41.8 (13.4)
Gender Males Females	 9 (18%) 40 (82%)
HIV[b], n (%) Positive Negative	 12 (24%) 37 (76%)
Laterality, n (%) Unilateral Bilateral	 11 (22%) 38 (78%)
Anatomical classification[§], n (%) Anterior Intermediate Posterior Panuveitis	 1 (2%) 1 (2%) 0 (0%) 47 (96%)
Course of uveitis[§] (n = 48), n (%) Acute Chronic Recurrent	 10 (21%) 35 (73%) 3 (6%)
Choroiditis type, n (%) Multifocal Serpiginous Diffuse Granulomas Nil	 34 (69%) 4 (8%) 3 (6%) 6 (13%) 2 (4%)
Tuberculin skin test, n (%) Negative Positive	 6 (12%) 43 (88%)
Quantiferon-TB Gold (n = 48), n (%) Negative Positive	 10 (21%) 38 (79%)
TB[c] PCR[d] (n = 48), n (%) Negative	 38 (79%)

Indeterminate	2 (4%)
Positive	8 (17%)
Viral PCR[d] (n =48), n (%)	
VZV[e]	0 (0%)
EBV[f]	1 (2%)
Negative	47 (98%)
Concomitant corticosteroid treatment, n (%)	
Oral	46 (94%)
Topical	44 (90%)
Periocular	6 (12%)
Remission (n = 35), n (%)	
Yes	15 (43%)
No	20 (57%)

[§] = According to Standardization of Uveitis Nomenclature (SUN) criteria. [a]TBU = Tubercular uveitis [b]HIV = Human immunodeficiency virus [c]TB = Tuberculosis
[d]PCR = polymerase chain reaction (*Mtb* detected by IS6110 and MPB64 [none detected by Gene Xpert])
[e]VZV = varicella zoster virus [f]EBV = Epstein-Barr virus

Using a multilevel mixed effects model for the analysis of repeated outcomes at the individual level, the TBU cases achieved significant resolution at 6 months post-diagnosis (OR=1.21; 95% CI, 1.03-1.41; *P*=0.017) (Table 5.2). Resolution was maintained at subsequent visits (Table 5.2). This relationship was significant in both the univariate and multivariate models.

Table 5.2 Individual Level Response Using Two-level Multilevel Mixed Effects model

Tubercular Uveitis			
Univariate multilevel mixed effects			
Predictor	**Odds ratio**	***P*-value**	**95% CI**
Visit (months)			
1.5	1.02	0.78	0.88-1.19
3	1.10	0.209	0.95-1.29

6	1.21	0.017	1.03-1.41
9	1.33	0.001	1.13-1.56
12	1.50	<0.001	1.26-1.78
15	1.58	<0.001	1.34-1.85
Multivariate multilevel mixed effects			
Predictor	**Odds ratio**	***P*-value**	**95% CI**
Visit (months)			
1.5	1.02	0.777	0.88-1.19
3	1.10	0.203	0.95-1.29
6	1.20	0.016	1.03-1.41
9	1.33	<0.001	1.13-1.56
12	1.50	<0.001	1.26-1.78
15	1.58	<0.001	1.34-1.85
Age	1.00	0.74	1.00-1.004
Sex	0.85	0.009	0.75-0.96

When using generalized estimating equations to assess the overall TBU population response (Table 5.3), the TBU population achieved significant resolution at 6 months post-diagnosis (OR=1.21; 95% CI, 1.05-1.39; *P*=0.008). Again, using this method of analysis resolution was maintained at subsequent visits (Table 5.3). This association was maintained in both the univariate and multivariate analyses (Table 5.3).

Table 5.3 Population Level Response Using Generalized Estimating Equation

Tubercular Uveitis			
Univariate generalised estimating equations			
Predictor	**Odds ratio**	***P*-value**	**95% CI**

Visit (months)			
1.5	1.02	0.757	0.89-1.17
3	1.10	0.163	0.96-1.27
6	1.21	0.008	1.05-1.39
9	1.33	<0.001	1.15-1.54
12	1.50	<0.001	1.28-1.76
15	1.58	<0.001	1.36-1.83
Multivariate generalised estimating equations			
Predictor	**Odds ratio**	***P*-value**	**95% CI**
Visit (months)			
1.5	1.02	0.757	0.89-1.17
3	1.10	0.163	0.96-1.27
6	1.21	0.008	1.05-1.39
9	1.33	<0.001	1.15-1.54
12	1.50	<0.001	1.28-1.76
15	1.58	<0.001	1.36-1.83
Age	1.00	0.809	0.996-1.01
Sex	0.85	0.053	0.72-1.00

A time-series plot, after multiple imputation, showed increasing number of TBU cases achieving resolution from 1.5 months through to 3-, 6-, 9-, 12-, and 15-months (Figure 5.1).

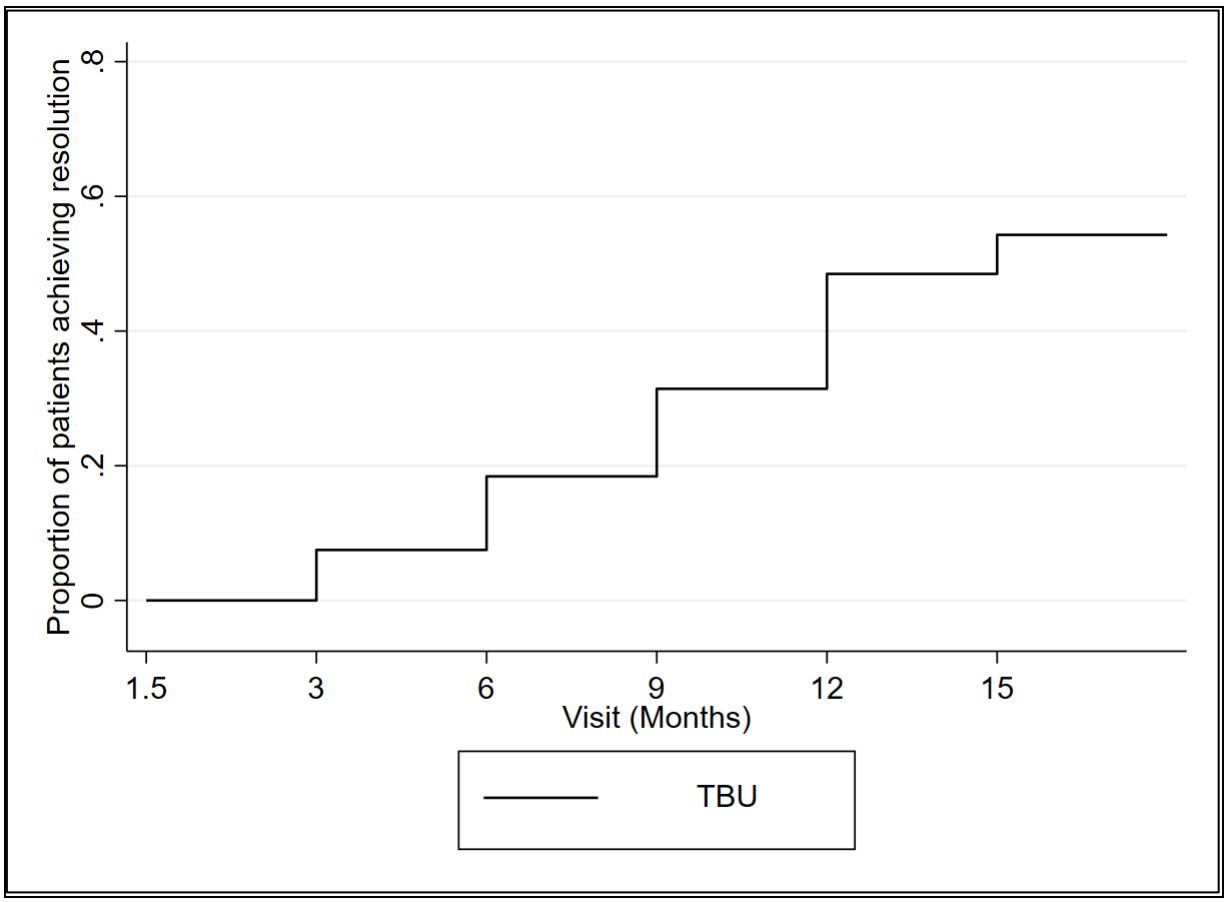


Figure 5.1 Proportion of tubercular uveitis (TBU) cases achieving resolution at follow-up visits

Using a multilevel mixed effects model for the analysis of repeated outcomes, the HIV-positive cases (OR=1.62; 95% CI, 1.13-2.31; *P*=0.008) and the HIV-negative cases (OR=1.25; 95% CI, 1.06-1.48; *P*=0.009) achieved significant resolution at 9 months post-diagnosis (Table 5.4).

Table 5.4 Univariate multilevel mixed effects model comparing the HIV-positive and HIV-negative tubercular uveitis (TBU) cases

HIV positive				**HIV negative**		
Univariate multilevel mixed effects						
Predictor	**Odds ratio**	**p-value**	**95% CI**	**Odds ratio**	**p-value**	**95% CI**
Visit (months)						
1.5	1.58	0.805	0.7-1.50	1.16	0.856	0.86-1.19

3	1.12	0.346	0.82-1.7	2.07	0.372	0.42-1.26
6	1.41	0.062	0.84-2.03	1.15	0.093	0.79-1.36
9	1.62	0.008	1.13-2.31	1.25	0.009	1.06-1.48
12	1.59	0.019	1.08-2.34	1.47	<0.001	1.23-1.76
15	1.77	0.003	1.22-2.57	1.52	<0.001	1.29-1.80

5.4 Discussion

Our study provides a timeframe for when a significant proportion of TBU cases will achieve resolution, and suggests a minimum duration required for ATT with corticosteroid medication to be effective.

Our study measured outcomes in terms of time to resolution of inflammation in TBU cases on 9 months ATT and corticosteroids. In both the models used for analysis, the odds of resolution of inflammation increased in the follow-up visits and reached statistical significance at 6 months post-diagnosis of TBU. Also, resolution was subsequently significantly maintained throughout the study.

The resolution of inflammation at 6 months in our study suggests that the minimum duration of ATT should be 6 months. However, since all the TBU cases in our study were treated for 9 months, we do not know if the same level of significance would have been maintained throughout the study if all participants had been treated with 6 months of ATT. Although studies in which TBU cases treated for 6 months with ATT reported good treatment outcomes (Manousaridis *et al.*, 2013; Balne *et al.*, 2014; Shakarchi, 2015a; Alli *et al.*, 2021), Ang et al. reported an eleven-fold decrease in the likelihood of recurrence of inflammation in TBU cases treated with ATT for ≥ 9 months compared to cases treated < 9 months (Ang *et al.*, 2012b). Anti-tubercular treatment is associated with significant adverse effects, including optic neuropathy, which can be minimized with a shorter duration of exposure to ATT (Gupta, Gupta and Rao, 2007). Therefore, it is important to determine if 6 months of ATT will have the same effect as 9 months of ATT. Large prospective cohort studies with longer follow-up comparing 6 months versus 9 months ATT are needed to compare the length of time significant resolution can be maintained.

Our study also highlights the issue regarding the concomitant use of corticosteroids to control inflammation in TBU. Corticosteroids were prescribed in 47 of the 49 TBU cases in our study. Concomitant corticosteroids are advocated to limit ocular tissue damage caused by the immune-mediated reaction to *Mtb* bacilli, *Mtb* antigens or retinal antigens (Gupta, Gupta and Rao, 2007; Basu *et al.*, 2015). Most studies report the use of corticosteroids, together with anti-tubercular medication, in the treatment of TBU; however, there is no standardization in the corticosteroid regimen (route, dose and duration) (Ang *et al.*, 2012b; Manousaridis *et al.*, 2013; Shakarchi, 2015a; Kee *et al.*, 2016). Although the corticosteroid regimen in our study varied, the outcome measured on corticosteroid treatment was standardized; resolution in our study was defined as minimal or no oral corticosteroids (≤10mg) according to the SUN classification (Jabs *et al.*, 2005).

The resolution of inflammation in the HIV-positive group and the HIV-negative group was achieved at 9 months post-diagnosis. However, there were a small number of cases in the two HIV groups (especially in the HIV-positive group); therefore, these results, although significant, should be treated with caution. To my knowledge there are no studies comparing resolution or recovery rates between these two groups. This needs to be explored in large prospective multicenter TBU studies. The small proportion of HIV-positive individuals diagnosed with TBU in our study highlights the issue of decreased sensitivity of the TST and QFT-G in immunosuppressed individuals (Huebner, Schein and Bass, 1993; Leidl *et al.*, 2010). Although a lower (≥ 5mm) TST measurement corrected for this, it is possible that TBU may have been underdiagnosed in HIV-positive individuals.

There was a higher proportion of TBU cases with chronic uveitis in our study. The chronicity highlights the reluctance of the physicians at our hospital to diagnose TBU and initiate ATT. Chronicity of uveitis, before ATT is started, is associated with poor visual outcomes due to complications (Patel *et al.*, 2013; Gunasekeran *et al.*, 2018; R. Agrawal *et al.*, 2020c). Thus, a lower threshold for the diagnosis of TBU, and initiation of ATT to control inflammation and prevent visual-impairing complications at our institution is needed.

The different anatomical classification types of TBU are associated with different treatment outcomes. Depending on the study, higher recurrence of inflammation has been associated with either anterior uveitis, intermediate uveitis or posterior uveitis (Bansal *et al.*, 2008; Ang *et al.*, 2012b; Tomkins-Netzer *et al.*, 2018). There was a high proportion of TBU cases that had panuveitis in our study, and this may have been due to referral bias from the General clinic to the Uveitis clinic at our hospital; cases with panuveitis and poor visual function may have preferably been referred for specialist assessment. Because of the very small number of cases

with the other anatomical classification types, it was not possible to do subgroup analysis comparing resolution between the different anatomical types.

Limitations of the study are: (1) the limited number of cases; (2) the limited follow-up; (3) the missing data in the follow-up visits; and (4) the concomitant corticosteroid-use. (1) The limited number of cases meant that subgroup analyses, such as comparing the different choroiditis types and anatomical phenotypes, was not possible. Although we compared the HIV groups, a meaningful conclusion could not be drawn because of the small number of cases in each group. (2) A longer follow-up would have enabled us to see for how long significant resolution would have been maintained. (3) Although there were missing data in the follow-up visits of the cases in the study, these were addressed by using multiple imputation in the statistical analyses. (4) Although corticosteroids were prescribed in most of the TBU cases, the outcome measure in terms of the resolution of inflammation (on ≤ 10 mg corticosteroids) was standardized according to the SUN criteria (Jabs *et al.*, 2005). Strengths of the study are that it is a prospective cohort study where the evaluation of all cases and collection of all the data were done by one Ophthalmologist (HA), and the ATT regimen and outcome measure were standardized.

5.5 Conclusion

Resolution of inflammation in TBU achieved at 6 months suggests that treating these cases with ATT for at least 6 months is advisable. Future large prospective cohort studies are needed to compare 6 months to 9 months of ATT to determine whether stopping treatment at 6 months will maintain resolution. Additionally, large prospective studies are warranted comparing resolution of inflammation between HIV-positive and HIV-negative individuals.

CHAPTER 6 INTEGRATED DISCUSSION AND CONCLUSION

In this thesis, there were several pertinent findings. The systematic review and meta-analysis revealed that the global prevalence of TBU among adult uveitis cases was 4.0% with an expectantly higher prevalence in high-burden countries (HBCs) (7.0%) especially in sub-Saharan Africa (11.0%). The overall treatment outcome globally, measured in terms of resolution or improvement of inflammation, was 82.0%. In the study in our setting, where the prevalence of HIV and TB is high, there was a high proportion (62.0%) of TBU in adult uveitis cases after exclusion of other causes of uveitis. A longitudinal follow-up of TBU cases on ATT (and corticosteroid treatment) showed that resolution occurred at 6 months post-diagnosis / post-treatment-onset; this response was maintained throughout the duration of the study. Additionally, there was a higher proportion of TBU cases (43%) in remission for the duration of 6 months after completion of 9 months of ATT.

Oher findings from our study were: 1) the high TST- (54%) and QFT-G- (50%) positivity, and the low TB-PCR-positivity (10%); 2) the significant association of female sex (odds ratio [OR]:5.1, *P*=0.002), negative HIV status (OR:0.2, *P*=0.001) and chronic uveitis (OR:4.1, *P*=0.008) with TBU; and 3) the higher proportion of the clinical phenotypes choroidal granulomas (13% versus 3%; *P* = 0.176) and serpiginous-like choroiditis (8% versus 0%; *P* = 0.292), and the lower proportion of the clinical phenotype diffuse choroiditis (6% versus 27%; *P* = 0.010), in the TBU group than the non-TBU.

The thesis highlights the difficulties in diagnosing TBU. Although diagnostic criteria for TBU, including suggestive clinical features of TBU, laboratory investigations, exclusion of other causes of uveitis and response to ATT, have been proposed, the diagnosis still remains challenging (Gupta, Gupta and Rao, 2007; Gupta *et al*., 2015). This is mainly due to the poor reliability of clinical features and laboratory methods in the diagnosis of TBU, and the lack of standardization of the diagnostic criteria of TBU. This is evident in the systematic review and meta-analysis where there was a high level of heterogeneity in determining the global prevalence of TBU. Although this was addressed by separating the studies into HBCs versus non-HBCs for TB, and into the different geographic regions, the intragroup heterogeneity was still considerable. This is probably due to the clinical and methodological diversity in studies within the sub-groups, especially the heterogeneity in the diagnostic criteria for TBU. We attempted to address this by pooling the studies with similar diagnostic criteria, but this did not reduce the level of heterogeneity.

The prevalence of TBU in the study in our setting (62.0%) was higher than the prevalence of the included studies (< 1.0% - 32%) in the systematic review and meta-analysis (Kotake *et al.*, 1996; Thean, Thompson and Rosenthal, 1996; Win *et al.*, 2017). However, direct comparison of the prevalence of TBU in our setting and the studies included in the systematic review and meta-analysis cannot be made for two reasons. Firstly, the prevalence of TBU in the included studies in the systematic review and meta-analysis was in a uveitis population that included other aetiologies, whereas in the study in our setting it was in a uveitis population that excluded other aetiologies; aetiologies that were excluded in our study included ARN, PORN, CMV retinitis, Behcet's disease, VKH, FHI, sympathetic ophthalmia, birdshot chorioretinopathy, MEWDS, APMPPE, PIC toxoplasmosis, syphilis, SLE, and sarcoid. The second reason is that the criteria for the diagnosis of TBU in the included studies in the systematic review and meta-analysis were stricter – the diagnosis in these studies were usually based on clinical features suggestive of TBU and a positive QFT-G or TST or both; whereas the criteria in the study in our setting were not restrictive – the diagnosis was based on any clinical features of uveitis (not restricted to clinical features suggestive of TBU) and a composite reference which included a positive QFT-G and /or TST and or TB-PCR.

Ocular clinical features suggestive of TBU is one of the diagnostic criteria used in the diagnosis of TBU. In the study in our setting, we did not use this criterion to make the diagnosis, since part of the objective of our study was to determine the ocular clinical features suggestive of TBU. Hence, we included cases with any clinical features of uveitis to determine the clinical features associated with TBU. The ocular clinical features suggestive of TBU in our study were serpiginous-like choroiditis and choroidal granulomas, albeit it not being significant. However, the sample size of the cases with these clinical phenotypes was small and a larger sample size may have shown significance. The COTS study group reported that serpiginous-like choroiditis and choroidal granulomas, with supporting immunological tests (TST and / or QFT-G), were strongly associated with TBU (Agrawal *et al.*, 2020b).

The difficulty in diagnosing TBU is compounded in HIV-positive cases. The sensitivity of TST and QGT-G in diagnosing TB is reduced in immunosuppressed individuals (Huebner, Schein and Bass, 1993; Leidl *et al.*, 2010). The study by Coebelens et al. has shown that even reducing the cut-off value from 10 mm to 5 mm has limited benefit in decreasing the false-negative TST results (Cobelens *et al.*, 2006). These studies are possibly supported by the findings of our study which showed a lower proportion of HIV positive cases in the TBU group (24%) than the non-TBU group (62%); also, a negative HIV test was significantly associated with TBU on both univariate and multivariate analyses. Since the diagnosis of TBU in our study was mainly based

on a positive QFT-G and / or TST, a lower proportion of TBU cases being HIV-positive may be due to the higher false negative TB tests secondary to immunosuppression. The higher false-negative may have been circumvented by using the T-spot.TB® (Oxford Immunotech, UK) test which is more sensitive in diagnosing TB in HIV-positive individuals with lower CD4+ cell counts (Bocchino *et al.*, 2009). This would have possibly yielded more TBU cases in our study; however, it is not available at our hospital. A study from Cape Town in South Africa also found a higher proportion of HIV negative cases (87%) diagnosed with intra-ocular TB (Smit, Esterhuizen and Meyer, 2018); the QFT-G test was used to support the diagnosis.

In the diagnosis of TBU, the TB-PCR-positivity of in-house PCR tests are low, varying from 37.7% - 58.8% (Gupta *et al.*, 1998; Arora *et al.*, 1999; Sudheer *et al.*, 2018; Agarwal *et al.*, 2019). In our study, the TB-PCR-positivity of the in-house PCR tests were lower (10%) than the above reported values. The low TB-PCR-positivity indicates that these tests, although helpful, are not reliable for the diagnosis of TBU. This is mainly because of the paucibacillary nature of TBU and the small ocular fluid sample. The Gene Xpert MTB/RIF assay in our study was not reliable nor helpful in the diagnosis of TBU and the screening of rifampicin resistance; the 1st 67 cases yielded successive negative results, and because of this we decided to stop further testing since the testing methodology was not optimized for the sample type and the associated cost. This version of the GeneXpert MTB/RIF assay had lower sensitivities for paucibacillary specimens (Vadwai et al., 2011; Penz et al., 2015). The latest version of the GeneXpert MTB/RIF, the Xpert Ultra, has been shown to display higher sensitivity albeit no improvement in specificity and rifampicin resistance detection (Opota et al., 2019).

The decision to initiate antitubercular treatment for TBU is challenging, given the difficulty in diagnosing this condition. Another challenging issue is the duration of ATT for an adequate response. It has been suggested that ATT for TBU should be stopped if there is no response within 4 months (Alvarez, Roth and Hodge, 2009; Vos *et al.*, 2013). However, studies have shown that a shorter ATT duration for TBU is inadequate for a good outcome in terms of the resolution of inflammation (Ang *et al.*, 2012b; Agrawal *et al.*, 2015). Our longitudinal study showed that a minimum of 6 months is needed to get significant resolution of inflammation. Although significant resolution was maintained throughout the duration (15 months) of the study on 9 months of ATT, we are not sure if 6 months of treatment would have maintained the same level of significance for the duration of 15 months. Our study also showed that remission was achieved in 43% of TBU cases treated with ATT. In the cases that did not respond to ATT, TB-drug resistance was considered as a potential reason for this. However, because of the

difficulty in diagnosing TBU, the low TB-PCR positivity of ocular fluid samples and the invasive nature of the procedure, the patients were not subjected to another sampling procedure.

Two other issues in the treatment of TBU are the concomitant use of corticosteroids and immune reconstitution syndrome. Most studies report the use of corticosteroids, together with anti-tubercular medication, to limit ocular damage in TBU; however, there is no standardization in the corticosteroid regimen (route, dose and duration) (Ang *et al.*, 2012b; Manousaridis *et al.*, 2013; Shakarchi, 2015a; Kee *et al.*, 2016). Forty-seven of the 49 TBU cases in our study were prescribed corticosteroids. Although the corticosteroid regimen in our study varied, the outcome measured on corticosteroid treatment was standardized; resolution in our study was defined as minimal or no oral corticosteroids (≤10mg) according to the SUN classification (Jabs *et al.*, 2005). Immune reconstitution syndrome in TBU cases treated with ATT has been described (Babu et al., 2006). Immune reconstitution syndrome was not seen in our cohort of TBU cases treated with ATT for two reasons: 1) All newly diagnosed HIV positive cases were treated with antiretroviral therapy 1 – 2 months after initiating ATT. 2) Concomitant corticosteroid treatment was initiated within 1 to 2 weeks after initiating ATT in 47 of the 49 TBU cases.

Central to the challenges in diagnosing and treating TBU, is the pathogenesis of TBU. The low *Mtb*-positivity in ocular samples (Gupta *et al.*, 1998; Arora *et al.*, 1999; Wroblewski *et al.*, 2011; Sudheer *et al.*, 2018; Agarwal *et al.*, 2019) and the concomitant use of corticosteroids to treat TBU (Kee *et al.*, 2016; Gupta, Gupta and Rao, 2007) indicates that direct invasion by the *Mtb* bacilli in the eye is not the only pathogenetic mechanism of TBU, but indirect immune-mediated mechanisms are also involved in the pathogenesis of TBU. There is evidence to suggest that indirect immune-mediated mechanisms, such as an immune reaction to non-viable *Mtb* bacilli or its products (proteins or ribonucleic acid) in the eye and / or an autoimmune reaction to ocular antigens (retinal antigens), play a role in the pathogenesis of TBU (Garip *et al.*, 2009; Basu, Elkington and Rao, 2020). This would explain the low yield of *Mtb* bacilli from the eye, the high QFT- and TST-positivity, and the need for concomitant anti-tubercular and corticosteroid treatment to remove the inciting *Mtb* bacilli and control inflammation, in our study.

The limitations of our prospective study were: (1) the limited number of cases in the subgroups; (2) the limited follow-up; and (3) the missing data in the follow-up visits. (1) The limited number of cases in the subgroups meant that, although differences in clinical signs and different choroiditis types were found between the TBU and non-TBU groups, statistical significance may not have been reached because of this. (2) A longer follow-up would have enabled us to

see for how long significant resolution would have been maintained. (3) Although there were missing data in the follow-up visits of the cases in the study, these were addressed by using multiple imputation in the statistical analyses.

This thesis has identified several areas for further research to better understand TBU. This includes addressing the diagnosis of TBU. especially the clinical predictors and the laboratory evaluation of TBU. Large multicentre prospective studies, with adequate cases in the clinical subgroups, are needed to determine the clinical predictors of TBU. To improve the diagnostic accuracy TBU, more studies involving newer PCR techniques with a lower LOD are needed. Another area of research that needs to be addressed is the comparison of 6 months versus 9 months of ATT to compare the length of time significant resolution of inflammation is maintained between the 2 groups. In addition, the pathogenesis of TBU needs to be further elucidated; better understanding of the pathogenesis may improve the diagnosis and treatment outcomes of TBU

In conclusion, the global prevalence of TBU is 4.0% with an expectantly higher prevalence (11.0%) in sub-Saharan Africa. The prevalence of TBU among uveitis cases after exclusion of other causes of uveitis in our setting is high (62.0%). Resolution of inflammation of TBU cases on ATT occurs at 6 months, indicating that this is the minimum period for which treatment should be prescribed.

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CHAPTER 8 APPENDIXES

Appendix 1: [PDF] Alli HD, Ally N, Mayet I, Dangor Z, Madhi SA. Global prevalence and clinical outcomes of tubercular uveitis: A systematic review and meta-analysis. *Surv Ophthalmol.* doi: 10.1016/j.survophthal.2021.10.001.

Appendix 2: [PDF] Alli HD, Ally N, Mayet I, Joseph L, Omar SV, Madhi SA. Epidemiology and clinical predictors of Tubercular Uveitis in a High TB and HIV South African Setting: A Prospective Cohort Study. *Tranl Vis Sci and Technol*.

Appendix 3: [PDF] Alli HD, Ally N, Mayet I, Joseph L, Omar SV, Madhi SA. Treatment Outcome of Tubercular Uveitis in a high TB and HIV setting: A Prospective Cohort Study. *Clin Ophthalmol*.

Appendix 4: Map outlining the six districts of Gauteng Province, South Africa.

Appendix 5: Map outlining the sub-districts/regions of the greater Johannesburg metropolitan area.

Appendix 6: Certificate of approval granted by the University of Witwatersrand Human Research Ethics Committee on the 28th September 2013 (HREC number: M120963).

Appendix 7: Turnitin similarity index.

Appendix 1

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Survey of Ophthalmology

Review article

Global prevalence and clinical outcomes of tubercular uveitis: a systematic review and meta-analysis

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ABSTRACT

Tubercular uveitis (TBU) is an inflammation/infection of the eye secondary to *Mycobacterium tuberculosis* infection. The difficulty in making the diagnosis has resulted in variable prevalence and clinical response rates. We aimed to determine the global prevalence of TBU in uveitis patients stratified by TB high-burden countries (HBCs) and non-HBCs and by geographic regions and the clinical response of TBU to antitubercular treatment

We performed a systematic review and meta-analysis of TBU studies published in PubMed, Scopus and EMBASE, up to June 30, 2020. A random effects model was used for all meta-analyses. Of 5,018 articles identified, 70 prevalence studies (65,607 uveitis and 3,166 TBU cases) and 18 clinical outcome studies (1,570 TBU cases; 1,304 responded to antitubercular therapy [ATT]) were analyzed. The overall weighted prevalence of TBU was 4.0% (95% CI, 3–5); in TB HBCs it was 7.0% (95% CI, 5–11), non-HBCs 3.0% (95% CI, 2–4), and sub-Saharan Africa 11.0% (95% CI, 8–15). The overall weighted clinical response was 82.0% (95% CI, 75–89). Despite the difficulty in diagnosing TBU, the prevalence is expectantly higher in HBCs, and sub-Saharan Africa and the clinical outcome is poor. Standardization of diagnostic criteria and ATT is warranted in future cohort studies.

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1. Background

Worldwide, 7 million new cases of tuberculosis (TB) were reported in 2018, 15% of which were extrapulmonary TB.[113] Intraocular tuberculosis commonly presents independent of the pulmonary manifestation of TB, and frequently (60–93%) presents as tubercular uveitis (TBU).[27,41] The prevalence of intraocular TB in individuals with pulmonary TB is between 1.4% and 6.8%.[27,41,70]

Tubercular uveitis (TBU) can result in ocular morbidity, including visual impairment, chronic hypotony, and blindness.[26,51,119] Delay in diagnosis, chronic disease, and posterior uveitis with choroiditis are associated with poor visual outcomes.[26,51,119] The reported prevalence of TBU among individuals with uveitis varies from 0.2% to 32%.[67,114] Understanding the pathogenesis of TBU is challenging. The original explanation that TBU results from hematogenous spread and direct invasion of local ocular tissues by *Mycobacterium tuberculosis* (*Mtb*) is oversimplistic. The lack of microbiological or molecular evidence of *Mtb* in ocular samples suggests that an immune reaction to *Mtb* antigens or nonviable *Mtb* bacilli in the eye may play a role.[25,44,116] Another possible explanation is that TBU is an autoimmune reaction whereby distal T-cell priming occurs due to a cross-reaction between *Mtb* and retinal antigens.[25,46]

The clinical signs suggestive of TBU described are broad-based posterior synechiae, severe vitritis, retinal vasculitis, serpiginous-like choroiditis, choroidal granuloma, and choroidal abscess.[15,22,52] More recently, the Collaborative Ocular Tuberculosis Study (COTS) identified serpiginous-like choroiditis and choroidal granulomas as being strongly associated with TBU in endemic and nonendemic regions.[8] Detection of *Mtb* by microscopy, culture or polymerase chain reaction (PCR) of ocular fluids (aqueous or vitreous humor) is the definitive method for diagnosing TBU.[55,118] Currently, PCR is the method of choice to diagnose TBU. In single-center studies, the PCR-positivity rate in TBU cases is between 37.7% and 58.8%.[19,54,105] In the COTS multicenter study, the reported TBU PCR-positivity rate was 55.9%.[4] In one study using multi-targeted PCR, where several genes (*IS6110, MPB64* and *protein b*) were simultaneously amplified, the PCR-positivity rate in TBU cases was reportedly higher (77.8%).[98] The variable and inconsistent diagnostic accuracy of PCR, and the possible "immune mediated" pathogenesis of TBU have led to the use of indirect immunological tests, such as the tuberculin skin test (TST) and interferon-gamma release assay (IGRA), in supporting the diagnosis of TBU.[74] These tests, however, have low sensitivities and specificities, and are unable to discriminate between latent and active TB.[16,21,57] Chest and ocular imaging rarely assist in making the diagnosis of TBU.[12,55,110] Since diagnostic tests are not singularly helpful, the diagnosis of TBU is often based on different combinations of the above investigations, together with suggestive clinical findings and clinical response to anti-tubercular treatment (ATT).[53,55,110] The lack of standardization in the diagnostic criteria of TBU and the poor reliability of laboratory methods have contributed to the large variations in the reported prevalence of TBU.[55]

The clinical outcomes, specifically the clinical response to ATT, during treatment and after its completion, are usually determined by measuring the improvement or resolution of inflammation in the eye. Variable clinical responses to ATT, as low as 24% and as high as 100%, have been reported.[14,77,97] Tubercular uveitis patients treated for 9 months or longer have been reported to have better clinical outcomes than those treated for 6 months.[7,14] Low-dose systemic and / or topical corticosteroids are often used in combination with multi-drug ATT, to control the inflammation and limit the damage to ocular tissues.

There is a paucity of literature on the prevalence of TBU globally. Furthermore, a systematic review on treatment outcomes for intraocular TB following ATT conducted in 2016,[62] did not analyze the effect of different anti-TB drug regimens on treatment outcome of TB. Also, the review, while stratifying analyses between Asian and non-Asian countries, did not compare the outcome of TBU between countries with a high burden of TB (HBCs) and non-HBCs, or between the 7 super-regions defined by the Global Burden of disease (GBD) study.[83,112]

We undertook a systematic review and meta-analysis on the prevalence of TBU diagnosis in individuals presenting with uveitis; and the clinical outcomes of TBU. We aimed to determine: (1) the overall prevalence of TBU, including stratification between HBCs and non-HBCs, between different GBD geographic regions, and between studies with data collection started before 2010 and studies with data collection started during or after 2010. (2) The response of TBU to ATT, including stratification between HBCs and non-HBCs. The year 2010 was arbitrarily chosen on the assumption that the 2007 Gupta and coworkers TBU diagnostic criteria would have been in widespread use by then.[55]

2. Methods

2.1. Study selection

All titles and abstracts were reviewed by 2 authors (HDA and IM), with a third author (SAM) adjudicating on conflicting results. Systematic and narrative reviews, animal studies, editorials and letters were excluded; h.owever, the reference lists of review papers were screened for studies that met inclusion criteria. The full texts of eligible studies / papers were then examined for inclusion into the prevalence or clinical outcome parts of the systematic review and meta-analysis. When data from the same cohort were reported in separate manuscripts, the study reporting the largest sample fulfilling our eligibility criteria was selected. If there were doubts regarding these datasets, contact with the corresponding authors was attempted for clarification.

2.2. Data collection and risk of bias assessment

Two authors (HDA and NA) extracted the data with disagreements resolved through discussion. Disagreements that persisted were resolved by a third author (IM). Data were extracted according to the aims of the systematic review and meta-analysis. Since we also determined the prevalence (1) in high-quality studies, (2) based on diagnostic criteria, (3)

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based on study design; and the clinical outcomes on different anti-TB drug regimen and treatment duration, the data were extracted accordingly. For prevalence, the following data were extracted from published studies: author, year, country, study design, total number of uveitis patients, mean age and standard deviation of uveitis patients, sex of uveitis patients, number of TBU patients, diagnostic criteria with or without ATT, and data quality (Table 1). For clinical outcomes, the following data were extracted from published studies: author, year, country, study design, mean age, and standard deviation of TBU patients, sex of TBU patients, number of TBU patients treated, number of TBU patients that responded to ATT, anti-TB drugs, ATT duration, and data quality (Table 2). The studies were classified as HBC or non-HBC for TB according to the World Health Organization (WHO) TB burden data.[113] The studies were divided into 7 GBD superregions: (1) High Income (North America, Southern Latin America, Western Europe, Asia-Pacific and Australasia), (2) Central Europe, Eastern Europe and Central Asia, (3) East Asia, South-East Asia and Oceania, (4) South Asia, (5) North Africa and Middle East, (6) Sub-Saharan Africa, and (7) Latin America and Caribbean.[83,112] The division of studies according to when data collection was started (before 2010 or during and after 2010) was arbitrary and based on the assumption that the criteria suggested by Gupta and coworkers would have taken a while to be applied to the studies before starting data collection.[55] Extracted data were stored in Microsoft Excel™ (Microsoft Corporation).

The quality and risk of bias of the included studies were assessed using a modified version of the Joanna Briggs Institute (JBI) critical appraisal tool.[81,82] The assessment scales were adapted to the relevant questions under review and are shown in Table 3. HDA and NA independently rated the quality of the studies with disagreements resolved through discussion and where necessary a third author (IM).

2.3. Data synthesis and analysis

Statistical analysis was performed using STATA 16.1 (Statacorp LLC, College Station, TX). A random-effects model was used to perform the meta-analysis. Subgroups were specified before statistical analysis based on TB high-burden countries (HBCs) and non-HBCs; geographical regions; studies with data collection started before 2010 and during or after 2010; study design; diagnostic criteria; and anti-TB drug regimen in terms of number of drugs and duration of ATT. Binary outcome data were analyzed using the "metaprop" command in STATA, and reported as proportions. The Freeman-Tukey double arcsine transformation was performed to normalize outcomes before pooling the prevalence. Study specific 95% confidence intervals were generated using the exact method. The I^2 statistic was used to check for overall, intergroup, and intragroup heterogeneity, and was classified as not important (0–40%), moderate (30–60%), substantial (50–90%), and considerable (75–100%) using the Cochrane guide.[33(p10)] Forest plots were then generated from the data. When the subanalysis was conducted for treatment outcome according to number of drugs or treatment duration, studies that did not indicate the number of drugs or treatment duration were excluded from this subanalysis. The weighted mean age was calculated using the "meta set" command and restricted maximum likelihood, from studies that provided a mean age and standard deviation, in addition to the total number of uveitis patients for prevalence and the total number of TBU for clinical outcomes. The weighted proportion of males to females was calculated using the "metaprop" command as stated above.

3. Results

3.1. Search results

Of 5,018 articles identified through the 3 database searches (Fig. 1), 280 articles were assessed for eligibility, and 85 articles (70 for prevalence and 18 for clinical outcome) were included. Three studies with clinical outcome data also contributed to data on prevalence of TBU in uveitis cases [77,84,97] (Table 1). All the studies reporting on prevalence of TBU were hospital-based, and 3 studies had sets of data from different time periods all of which were included (Table 1).[67,69,100] All 18 studies reporting on clinical outcomes were hospital-based (Table 2).

3.2. Studies reporting on prevalence of TB uveitis

Of the 70 studies reporting on prevalence of TBU, 50 (71%) were case series, 10 (14%) crosssectional, 9 (13%) cohort studies and 1 (2%) a case-control study (Table 1). Twenty-five (36%), 29 (41%) and 13 (19%) of the studies were of high, medium, and low quality, respectively (Table 1). Twenty-two studies (31%) were from TB HBCs (including 8 from India), and 48 (69%) studies were from non-HBCs, of which 5 each were from Japan and Saudi Arabia (Table 1 and Fig. 2h). Twenty-seven studies were from countries in the igh-income region (North America, Western Europe, Asia-Pacific, Australasia, and Southern Latin America), 10 from the East Asia, South-East Asian, and Pacific region, 11 from the South Asia region, 17 from the North Africa-Mediterranean region, 2 from the sub-Saharan Africa region, and 2 from the Latin America and Caribbean region (Table 1 and Fig. 3). Data collection was started before 2010 in 53 studies, and during or after 2010 in 19 studies (Fig. 4); 2 studies (Siak and coworkers[100] and Kunimi and coworkers[69]) had 2 sets of data, of which 1 was collected before 2010, and the other during or after 2010.[69,100] Of the 25 high-quality studies, 18 were from non-HBCs and 7 were from HBCs (Fig. 5).

Nineteen studies had no diagnostic criteria for TBU.[32,39,43,48,49,59–61,67,71,88,90,92,93,95,96,107,108,117] There were 18 studies that had diagnostic criteria that included response to ATT[3,9–11,23,34,35,45,56,58,72,85,86,100,102,109,111,114]; only 4 (22.2%) of these studies[35,100,102,109] had microbiological/molecular analysis of intraocular fluid as part of the diagnostic criteria. Twenty-nine studies[2,17,28–31,38,40,50,63–66,69,76–79,84,89,97,101,103,104,106,115,119–121] had diagnostic criteria, but did not include response to ATT, 11 (38%)[28,29,40,50,69,76,77,84,89,104,106] of which had microbiological/molecular analysis of intraocular fluid as part of the diagnostic criteria. Four studies[1,75,87,91] used criteria mentioned in the review articles by Gupta and coworkers[53,55], albeit it being unclear as to which criteria were used.

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Table 1 – Study characteristics of prevalence studies.

	Study author (year)	Study design	R/P[1]	Country of study	HBC[2] yes/no	Uveitis patients; n=	Mean age in years	SD[3]	Sex Malen (%)	TB uveitis patientsn=	Diagnosticcriteria used yes/no	ATT[4] yes/no	Data quality-Low/Med[5]/High
1	Biswas et al. (1996-1997)[29]	Case series	R	India	Yes	1273			792 (62)	7	Yes	No	Med
2	Kotake* et al. (1996)[67]	Case series	R	Japan	No	407	40•7		179 (44)	1	No	No	Med
		Case series	R	Japan	No	551	46•5		237 (43)	1	No	No	Med
3	Thean et al. (1996)[108]	Case series	R	UK	No	712	39•2		371 (52)	2	No	No	Med
4	Rodriguez et al. (1996)[92]	Case series	R	USA	No	1237	39•8	16•2	512 (41)	8	No	No	Med
5	Merrill et al. (1997)[78]	Case series	R	USA	No	385			148 (38)	2	Yes	No	High
6	Islam and Tabbara (2002)[58]	Case series	R	Saudi Arabia	No	200	38	16	120 (60)	21	Yes	Yes	High
7	Singh et al (2004)[102]	Case series	R	India	Yes	1233			641 (52)	125	Yes	Yes	Med
8	Soheilian et al. (2004)[104]	Cross-sectional		Iran	No	544	34•3	15•4	238 (44)	8	Yes	No	High
9	Sengun et al. (2005)[96]	Case series	R	Turkey	No	300	35•7		162 ((54)	4	No	No	Med
10	Yang et al. (2005)[117]	Case series	R	China	Yes	1752	33•8	16•5	902 (52)	13	No	No	Med
11	Goto et al. (2007)[69]	Cross-sectional		Japan (Multicentre)	No	3060				20	No	No	Low
12	Khairallah et al. (2007)[64]	Cohort	R	Tunisia	No	472			224 (47)	5	Yes	No	High
13	Rathinam et al. (2007)[90]	Case series	R	India	Yes	8759	36•5	15•5	5451 (62)	488	No	No	Low
14	Kazokoglu et al. (2008)[61]	Cross-sectional		Turkey (Multicentre)	No	761	35•4	15•3	388 (51)	3	No	No	Low
15	Das et al. (2009)[38]	Case series	R	India	Yes	308			209 (68)	9	Yes	No	High
16	Hamade et al. (2009)[56]	Case series	R	Saudi Arabia	No	488	38		264 (54)	37	Yes	Yes	High
17	Jakob et al. (2009)[59]	Case series	R	Germany	No	1686			752 (45)	21	No	No	Low
18	Keino et al. (2009)[63]	Case series	R	Japan	No	834			352 (42)	36	Yes	No	High
19	Miyanaga et al. (2009)[79]	Case series	R	Japan	No	1338	50•5	17•7	526 (39)	5	Yes	No	High

(continued on next page)

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Table 1 (*continued*)

	Study author (year)	Study design	R/P[1]	Country of study	HBC[2] yes/no	Uveitis patients; n=	Mean age in years	SD[3]	Sex Malen (%)	TB uveitis patientsn=	Diagnosticcriteria used yes/no	ATT[4] yes/no	Data quality-Low/Med[5]/High
20	Ball et al. (2010)[23]	Cross-sectional		France	No	108	49•4	19•1		13	Yes	Yes	High
21	Nora et al. (2012)[86]	Case series	R	Indonesia	Yes	1004				39	Yes	Yes	Med
22	Manousaridis et al. (2013)[77]	Cohort	R	UK	No	1360				21	Yes	No	¶
23	Nizamuddin et al. (2013)[85]	Case series	R	Saudi Arabia	No	587	34•8	12•8	319 (54)	6	Yes	Yes	Med
24	Sittivarakul et al. (2013)[103]	Case series	R	Thailand	Yes	254	42•6	17	140 (55)	3	Yes	No	High
25	Vos et al. (2013)[111]	Case series	R	Netherlands	No	575				11	Yes	Yes	Med
26	Yeo et al. (2013)[119]	Case series	R	Singapore	No	359			206 (57)	24	Yes	No	High
27	Ang et al. (2014)[17]	Cohort	P	Singapore	No	102	48•2	16•7		23	Yes	No	High
28	Cakar-Ozdal et al. (2014)[32]	Case series	R	Turkey	No	1028	36•2	14•9	598 (58)	6	No	No	Low
29	Rahimi et al. (2014)[88]	Cross-sectional		Iran	No	475	30•5	15•14	216 (45)	2	No	No	Med
30	Roy et al. (2014)[93]	Case-control	R	Canada	No	43	32•1	15•4	9 (21)	2	No	No	Low
31	Tognon et al. (2014)[109]	Cohort	P	Italy	No	351				45	Yes	Yes	Med
32	Abdulaal et al. (2015)[3]	Case series	R	Lebanon	No	209	36	18	91 (44)	12	Yes	Yes	High
33	Al-Dhahri et al. (2015)[9]	Case series	R	Saudi Arabia	No	642	36•4	16•1	295 (46)	114	Yes	Yes	High
34	Das et al. (2015)[39]	Case series	R	India	Yes	343			209 (61)	60	No	No	Low
35	Engelhard et al. (2015)[43]	Cohort	R	USA	No	491				1	No	No	Med
36	Grajewski et al. (2015)[50]	Case series	R	Germany	No	474			213 (45)	1	Yes	No	High
37	Jones et al. (2015)[60]	Case series	R	UK	No	3000			1377 (46)	99	No	No	Low
38	Kianersi et al. (2015)[65]	Case series	R	Iran	No	2016	33•8	10•56	915 (45)	4	Yes	No	High
39	Kilic et al. (2015)[66]	Case series	R	Turkey	No	140	39•6	14•9	79 (56)	1	Yes	No	Med
40	Liberman et al. (2015)[72]	Case series	R	Chile	No	611			256 (42)	14	Yes	Yes	Med

(*continued on next page*)

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Table 1 (*continued*)

	Study author (year)	Study design	R/P[1]	Country of study	HBC[2] yes/no	Uveitis patients; n=	Mean age in years	SD[3]	Sex Malen (%)	TB uveitis patientsn=	Diagnosticcriteria used yes/no	ATT[4] yes/no	Data quality-Low/Med[5]/High
41	Llorenc et al. (2015)[75]	Cross-sectional		Spain	No	1022			465 (46)	54	Gupta		Low
42	Shakarchi et al. (2015)[97]	Cohort	P	Iraq	No	506				64	Yes	No	¶
43	Silpa-Archa et al. (2015)[101]	Case series	R	Thailand	Yes	446	42•6	16•1	206 (46)	10	Yes	No	Med
44	Zheng et al. (2015)[121]	Case series	R	China	Yes	199	41	15•1	134 (67)	2	Yes	No	High
45	Schaftenaar et al. (2016)[95]	Cross-sectional		South Africa (Multicentre)	Yes	103			37 (36)	18	No	No	Low
46	Teixeira et al. (2016)[107]	Case series	R	Brazil	Yes	403			199 (49)	12	No	No	Med
47	Abano et al. (2017)[1]	Case series	R	Philippines	Yes	595	38•5	18•9	271 (0.45)	70	Gupta		Low
48	Al-Dhibi et al. (2017)[10]	Cohort	R	Saudi Arabia	No	888			390 (44)	94	Yes	Yes	Med
49	Chen et al. (2017)[35]	Case series	R	Taiwan	No	450	41•7	15•9	240 (53)	3	Yes	Yes	Med
50	Dogra et al. (2017)[40]	Case series	R	India	Yes	1807			1046 (58)	438	Yes	No	High
51	Gao et al. (2017)[45]	Case series	R	China	Yes	606	33•8	15•5	291 (48)	11	Yes	Yes	High
52	Gonzalez-Fernandez et al. (2017)[48]	Cross-sectional		Brazil	Yes	1053	39•8	17•8	455 (43)	55	No	No	Med
53	Lee et al. (2017)[71]	Case series	R	South Korea (Multicentre)	No	602	45•1	16•5	314 (52)	10	No	No	Low
54	Manandhar et al. (2017)[76]	Case series	R	Nepal	No	1113			567 (51)	45	Yes	No	Med
55	Ng et al. (2017)[84]	Cohort	R	New Zealand	No	1207				39	Yes	No	¶
56	Siak+ et al. (2017)[100]	Case series	R	Singapore	No	1249	45•8	16	639 (51)	84	Yes	Yes	High
		Case series	P	Singapore	No	148			80 (54)	6	Yes	Yes	High
57	Sukavatcharin et al. (2017)[106]	Cross-sectional		Thailand	Yes	758	45•6	16•6	357 (47)	65	Yes	No	Med
58	Win et al. (2017)[114]	Case series	R	Myanmar	Yes	139			71 (51)	45	Yes	Yes	High

(*continued on next page*)

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Table 1 (*continued*)

	Study author (year)	Study design	R/P[1]	Country of study	HBC[2] yes/no	Uveitis patients; n=	Mean age in years	SD[3]	Sex Malen (%)	TB uveitis patientsn=	Diagnosticcriteria used yes/no	ATT[4] yes/no	Data quality-Low/Med[5]/High
59	Wong et al. (2017)[115]	Case series	R	New Zealand	No	1148			621 (54)	36	Yes	No	Med
60	Zagora et al. (2017)[120]	Case series	R	Australia (Multicen-tre)	No	1165	51		650 (56)	49	Yes	No	High
61	Al-Baker et al. (2018)[11]	Case series	R	Qatar	No	310	39•3	14•2	186 (60)	45	Yes	Yes	High
62	Biswas et al. (2018)[28]	Case series	R	India	Yes	352				79	Yes	No	Med
63	Brydak-Godowska et al. (2018)[31]	Case series	R	Poland	No	279	38•3	15•3	107 (38)	2	Yes	No	Med
64	Chen et al. (2018)[34]	Case series	R	Singapore	No	1978			1185 (60)	148	Yes	Yes	High
65	Pandey et al. (2018)[87]	Cohort	P	Nepal	No	1140				12	Gupta		Med
66	Rahman et al. (2018)[89]	Case series	R	Bangladesh	Yes	652	32•3	12•4	340 (52)	70	Yes	No	High
67	Abd El Latif et al. (2019)[2]	Case series	R	Egypt	No	1315	34•8	11•9	702 (53)	202	Yes	No	Med
68	Rautenbach et al. (2019)[91]	Case series	R	South Africa (Mul-ticentre)	Yes	198	38		93 (47)	16	Gupta		Low
69	Borde et al. (2020)[30]	Cross sectional		India	Yes	210	46•6	11•2	107 (51)	25	Yes	No	Med
70	Kunimi* et al. (2020)[69]	Case series	R	Japan	No	1507			697 (46)	21	Yes	No	Med
		Case series	R	Japan	No	1587			707 (45)	19	Yes	No	Med

Data quality: Assessment of quality of study for prevalence modified from the Joanna Briggs Institute (JBI) critical appraisal tool.[82]
Gupta criteria: Diagnostic criteria according to Gupta et al review articles[53,55] but criteria not specified in these studies.

[1] R/P = retrospective/prospective.
[2] HBC = high-burden-country for TB defined by the WHO.[113]
[3] SD = standard deviation.
[4] ATT = antitubercular treatment.
[5] Med = medium.
* Studies with two data sets.
¶ Studies rated for clinical outcomes (see Table 2).

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Table 2 – Study characteristics of clinical outcome studies.

	Study author (year)	Study design	R/P[1]	Country of study	HBC[2]	All TBU[3]	Mean age All TBU[3]	SD[4] All TBU[3]	Sex Male All TBU[3]	Number of TBU[3] patients treated	Number of TBU[3] patients responded to treatment	Intensive phase ATT[5] drugs R[6]/H[7]/Z[8]/E[9]/M[10]	Total ATT[5] Duration (months)	Data quality Low/Med[11]/High
1	Gupta et al. (1998)[54]	Cohort	P	India	Yes					10	9	RHZ	≥ 9	Med
2	Babu et al. (2009)[20]	Cohort	R	India	Yes	51	40•5	11•5	27	49	41	RHZE	≥ 9	Med
3	Sanghvi et al. (2011)[94]	Cohort	R	UK	No	45				27	19	RHZE	6	Med
4	Ang et al. (2012)[14]	Cohort	R	Singapore	No					46	11	RHZE	Varied	Med
6	Manousaridis et al. (2013)[77]	Cohort	R	UK	No	21	46		15	16	16	RHZE	6	Med
6	Balne et al. (2014)[24]	Cohort	R	India	Yes	114	33•7	12•7	71	71	65	ŦŦ	6	Med
7	Agrawal et al. (2015)[7]	Cohort	R	UK	No	375				175	135	RHZE or RHZM	Varied	Med
8	Shakarchi et al. (2015)[97]	Cohort	P	Iraq	No	64	35•7		29	64	64	RHZE	6	High
9	Agrawal et al. (2017)[6]	Cohort	R	Muticenter (COTS-1)		801	40•5	14•8	413	801	699	ŦŦ	ŧ	High
10	Damato et al. (2017)[37]	Cohort	R	UK	No	54	44		33	41	33	RHZE or RHZ or RZE or RH or RE	Varied	Med
11	Ng et al. (2017)[84]	Cohort	R	New Zealand	No	39			17	24	16	RHZE or RHZM or RHZ	Varied	Med
12	Ang et al. (2018)[13]	Cohort	R	Singapore	No	62				36	25	RHZE	Varied	Med
13	Anibarro et al. (2018)[18]	Cohort	R	Spain	No	24	48•3	10•6	15	23	21	3- or 4-drug ATT	6	Med
14	Chung et al. (2018)[36]	Cohort	R	China	Yes					14	13	RHZE	Varied	High
15	Krassas et al. (2018)[68]	Cohort	R	UK	No	91				48	29	RHZE	6	Med
16	Sudheer et al. (2018)[105]	Cohort	R	India	Yes					34	30	RHZE	6	Med
17	Ghauri et al. (2019)[47]	Cohort	P	Pakistan	Yes	40	36	3	16	40	32	RHZE	≥ 9	High
18	Llorenc et al. (2020)[73]	Cohort	R	Spain	No	93				51	46	RHZE	Varied	Med

Data quality = Assessment of quality of study for clinical outcome modified from the Joanna Briggs Institute (JBI) critical appraisal tool.[81]
Varied = studies in which ATT duration was < 9 months in some patients and ≥9 months in others.
[1] R/P = retrospective/prospective.
[2] HBC = high-burden country for TB defined by the WHO[113]
[3] TBU = tuberculous uveitis.
[4] SD = standard deviation.
[5] ATT = antitubercular treatment.
[6] R = rifampicin.
[7] H = isoniazid.
[8] Z = pyrazinamide.
[9] E = ethambutol.
[10] M = moxifloxacin.
[11] Med = medium.
Ŧ = Number and names of ATT drugs not stated in study.
ŧ = ATT duration not stated in study.

[m5G;November 11, 2021;21:11]

Table 3 – Assessment of quality of the studies modified from the Joanna Briggs Institute (JBI) critical appraisal tools.[81,82]

Prevalence			
		Yes	No
1	Were study subjects and setting described in detail?		
2	Were valid methods used for the identification of the condition?		
3	Was the condition measured in a standard, reliable way for all participants?		
4	Did the study have consecutive inclusion of participants?		
5	Did the study have complete inclusion of participants?		
6	Was there clear reporting of the demographics of the participants in the study?		
7	Was there clear reporting of the prevalence numbers (%) of the condition?		
	Quality: 0-3 = Low 4–5 = Medium 6–7 = High		
Clinical outcome			
		Yes	No
1	Were there clear criteria for inclusion in the study?		
2	Were valid methods used for the identification of the condition?		
3	Was the condition measured in a standard, reliable way for all participant?		
4	Did the study have consecutive inclusion of participants?		
5	Did the study have complete inclusion of participants?		
6	Was there clear reporting of the demographics of the participants in the study?		
7	Was there clear reporting of clinical information of the participants?		
8	Were the outcomes or follow-up results of cases clearly reported?		
9	Was there clear reporting of the presenting site(s)/hospital(s)?		
10	Specific anti-TB drugs used and duration of treatment?		
	Quality: 0–3 = Low 4–7 = Medium 8–10 = High		

3.3. *Prevalence of TB uveitis in a population of uveitis patients*

Among the 70 studies reporting on 65,607 uveitis cases, 3,166 (4.8%) cases were TBU (Table 1). The weighted mean age of uveitis cases (means reported in 32 studies) was 39.3 (95% CI, 37.2–41.4) years; and 50.0% (95% CI, 48–52) of cases in whom gender was reported were males. The overall weighted prevalence of TBU among uveitis cases was 4.0% (95% CI, 3–5) (Fig. 2). The pooled weighted prevalence for high-burden countries (HBCs) was 7.0% (95% CI, 5–11) (range: 1.0%–32.0%) and non-HBCs 3.0% (95% CI, 2–4) (range: <1.0–23.0%) (Fig. 2); with "considerable" intergroup heterogeneity ($I^2 = 97.92\%$, $P < 0.01$). The pooled weighted prevalence for, the high-income region was 3.0% (95% CI, 2–4), the East Asia, South-East Asia, and Oceania region 4.0% (95% CI, 2–8), South Asia region 8.0% (95% CI, 4–14), North Africa and Middle East region 4.0% (95% CI, 2–8), sub-Saharan Africa region 11.0% (95% CI, 8–15), and Latin America and Caribbean region 5.0% (95% CI, 4–6) (Fig. 3). The pooled weighted prevalence of studies in which, data collection started before 2010 was 3.0% (95% CI, 2–4), and data collection started during or after 2010 was 8.0% (95% CI, 4–12) (Fig. 4).

The overall weighted prevalence of TBU in the high-quality studies was 6.0% (95% CI, 3–9) (Fig. 5). The pooled weighted prevalence in high-quality studies for HBCs was 8.0% (95% CI, 2–18) and non-HBCs was 5.0% (95% CI, 3–8). The pooled weighted prevalence of TBU in studies with no diagnostic criteria; diagnostic criteria that excluded ATT; and diagnostic criteria that included ATT was 2.0% (95% CI, 1–3); 4.0% (95% CI, 2–6); and 7.0% (95% CI, 5–10), respectively (Fig. 6). The weighted prevalence of the 4 studies that mentioned diagnostic criteria proposed by Gupta and coworkers,[53,55] but did not specify the criteria, was 6.0% (95% CI, 2–12). The weighted prevalence of TBU varied with study design and was similar at 4.0% (95% CI, 3–5), 5.0% (95% CI, 2–8) and 5.0% (95% CI, 2–9) for case series, cross-sectional and cohort studies, respectively (Fig. 7).

3.4. *Clinical outcomes of TB uveitis patients treated with antitubercular medication*

The 18 studies reporting clinical outcomes are summarized in Table 2. The weighted mean age of TBU patients (means reported in 5 studies) was 39.6 (95% CI: 33.0–44.3) years, and 54% (95% CI,48–59) were of male gender (reported in 9 studies). Fifteen of the studies were retrospective, and only 3 prospective cohorts (Table 2). Six (33%) of the studies were from TB HBCs (4 from India), and 11 (61%) were from non-HBCs (5 from the United Kingdom) (Table 2). One study was multicentered.

The quality of the studies was high and medium in 4 (22%)[6,36,47,97] and 14 (78%)[7,13,14,18,20,24,37,54,68,73,77,84,94,105] studies, respectively (Table 2). Cases in 12 studies[7,13,14,20,36,47,68,73,77,94,97,105] were treated with 4-drug ATT for the initial 2 months (Table 2). In 11 studies[13,14,20,36,47,68,73,77,94,97,105] this consisted of rifampicin (R), isoniazid (H), pyrazinamide (Z) and ethambutol (E) for the initial 2 months with oxifloxacin (M) replacing ethambutol in a few cases in 1 study.[7] The number of ATT drugs was 3 (RHZ) in 1 study[54], not mentioned in 2 studies[6,24] and varied between cases in 3 studies[18,37,84] (Table 2). The use of ocular and/or systemic corticosteroids was reported in all

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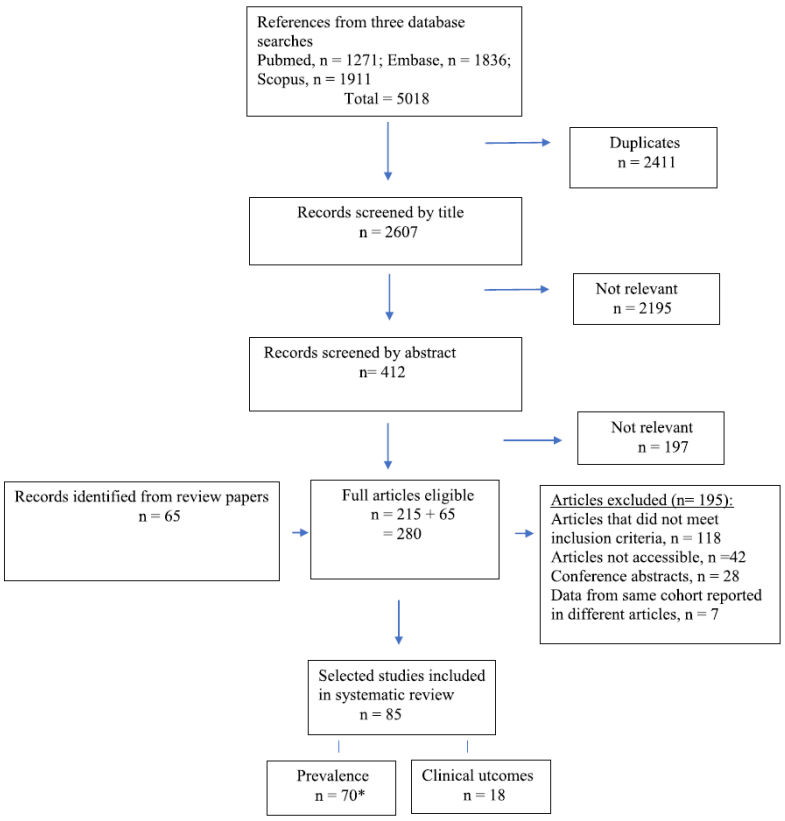


Fig. 1 – Flow diagram of literature search and results of selected studies.
***Three studies with clinical outcome data contributed to data on prevalence of TBU in uveitis cases.**

the studies. Duration of ATT was 6 months in 7 (39%) studies,[18,24,68,77,94,97,105] and ≥9 months in 3 (17%) studies[20,47,54] (Table 2). In 7 (39%) studies, there was intrastudy variation of ATT duration.[7,13,14,36,37,73,84] Treatment duration was not mentioned in 1 (5%) study.[6]

A total of 1,570 TBU cases were treated for TB, of whom 1,304 (83.1%) responded to ATT. The overall weighted clinical (inflammatory) response of TB uveitis cases treated with ATT was 82.0% (95% CI, 75–89) (range: 24.0%–100.0%) (Fig. 8). The pooled weighted response to ATT in TB HBCs was 88.0% (95% CI, 83–92) and 79.0% (95% CI, 64–91) in non-HBCs (Fig. 8). While there was "considerable" intragroup heterogeneity in the non-HBC group for response to ATT ($I^2 = 92.56\%$, $P < 0.01$), this was "not important" in HBC settings ($I^2 = 0.00\%$, $P = 0.60$). Five studies from HBCs had response to ATT above the weighted mean overall response of 82.0% (Fig. 8).

The pooled weighted response for studies with duration of ATT ≥9 months and 6 months was 83.0% (95% CI, 75–91) and 89.0% (75–98), respectively (Fig. 9). The pooled weighted response for the studies in which treatment duration varied was 73.0% (95% CI, 55–87). The pooled weighted response for studies with 3-drug ATT regimen and 4-drug ATT regimen was 90.0% (95% CI, 55–100), and 81.0% (95% CI, 68–91), respectively (Fig. 10). Studies in which the number of ATT drugs varied between cases had a weighted pooled response of 80.0% (95% CI, 66–92).

4. Discussion

The global prevalence of TBU in individuals presenting with uveitis was 4.0%, with an expectantly higher pooled prevalence in TB HBCs (7.0%) than non-HBCs (3.0%).[113] To determine a stronger reliable estimate of overall prevalence, we pooled the high-quality studies and observed a prevalence of 6.0%. In terms of the geographic prevalence, sub-Saharan Africa had a significantly higher (11.0%) TBU prevalence than the high-

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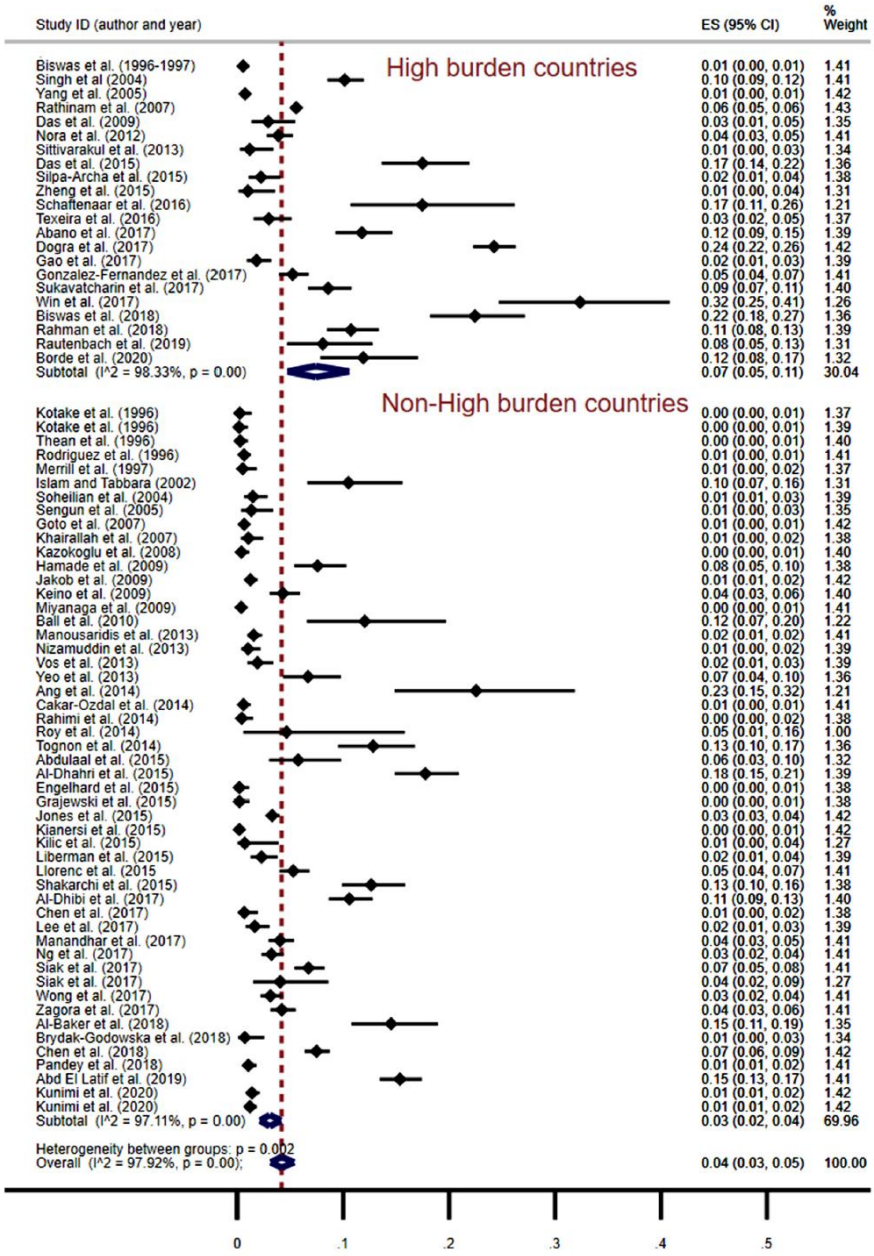


Fig. 2 – Meta-analysis of prevalence stratified by high-burden countries (HBCs) and non-high-burden countries (non-HBCs) for TB.

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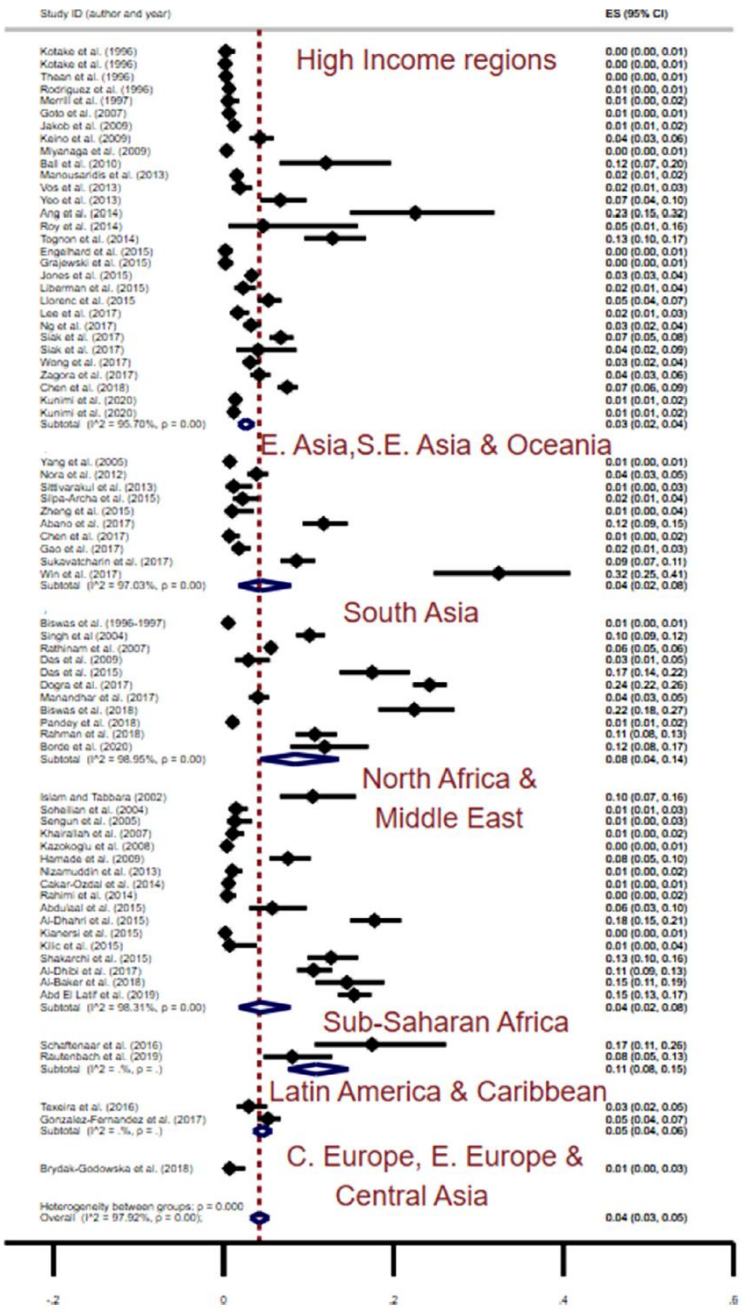


Fig. 3 – Meta-analysis of prevalence studies stratified by seven geographic super-regions defined by the Global Burden of Disease Study.[83,112]

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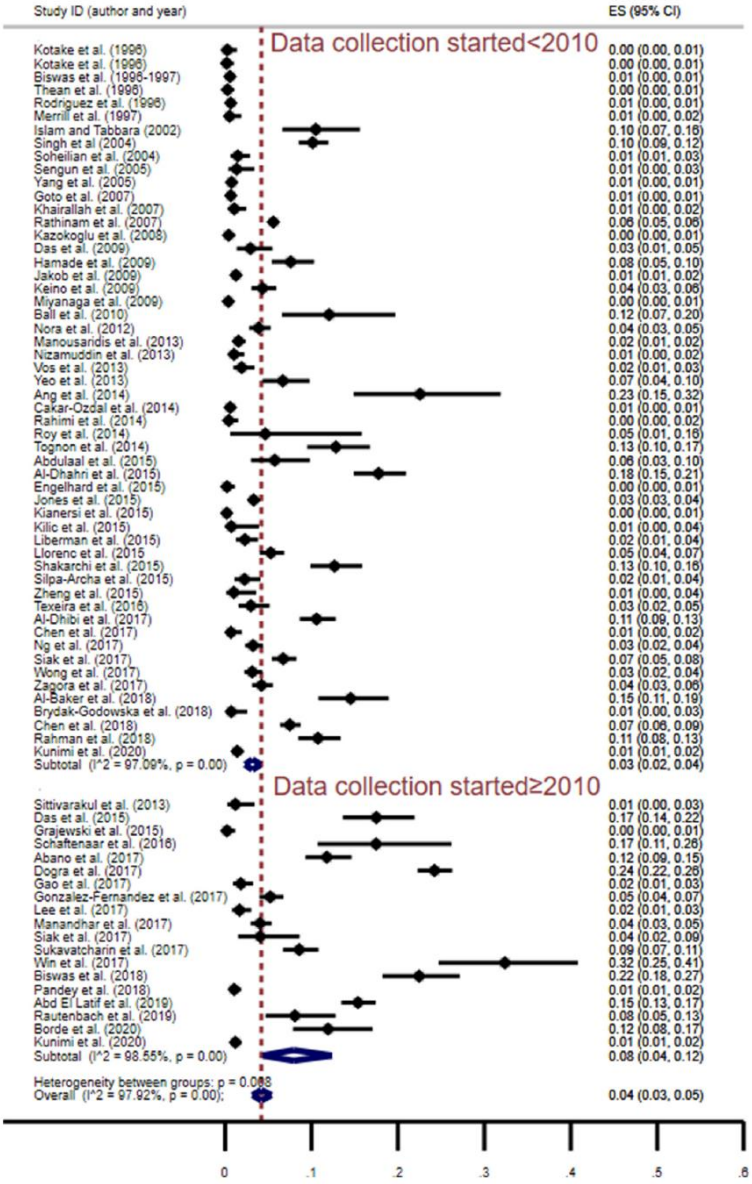


Fig. 4 – Meta-analysis of prevalence studies stratified by data collection started before (<) 2010 and data collection started during or after (≥) 2010.

income region (3.0%) and the Latin America and Caribbean region (3.0%). This is to be expected since sub-Saharan Africa has a higher prevalence of TB than these regions.[113] Studies in which data collection started during or after 2010 had a higher TBU prevalence (8.0%) than those in which data collection started before 2010 (3.0%), albeit it not being significant. This may have been due to widespread application of the combination of diagnostic criteria proposed by Gupta and coworkers from 2010 onward.[55] Overall, there was a considerable level of heterogeneity. This was addressed by separating

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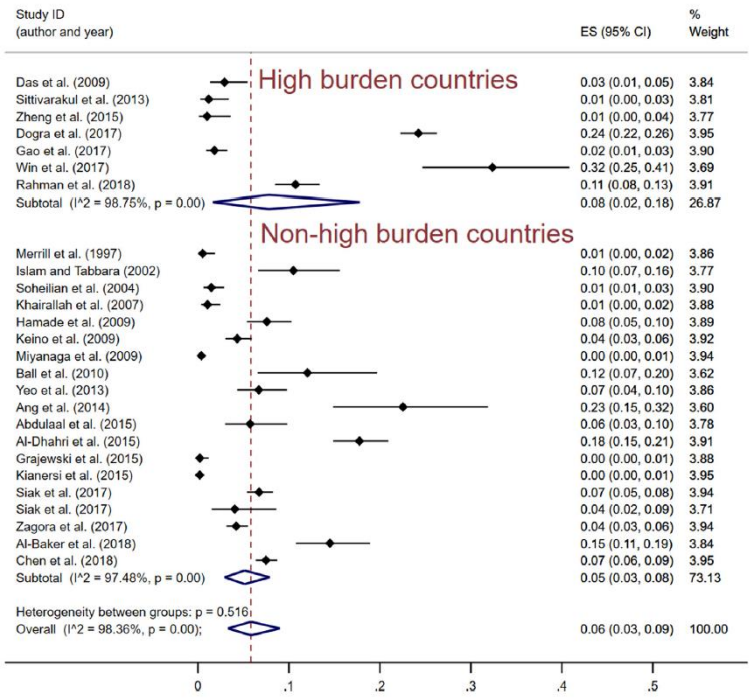


Fig. 5 – Meta-analysis of prevalence of TB Uveitis of high-quality studies.

the studies into HBCs versus non-HBCs for TB, into the different geographic regions, and into studies with data collection before 2010 and during or after 2010. Despite this, the intragroup heterogeneity was still considerable. This may be due to the clinical and methodological diversity in studies within the subgroups, especially the heterogeneity in the diagnostic criteria for TBU. We attempted to address this by pooling the studies with similar diagnostic criteria, but this did not reduce the level of heterogeneity.

Response to ATT has been suggested as a surrogate for the diagnosis of TBU,[7] and its inclusion in the diagnostic criteria algorithm may assist in improving estimates of the prevalence of TBU in uveitis cases. There may be merit in this statement as studies that included ATT as part of the diagnostic criteria had a significantly higher prevalence (8.0%) than studies with no defined diagnostic criteria (2.0%). There was considerable heterogeneity within the diagnostic criteria groups with ATT and without ATT; this may be due to the heterogeneity in the clinical signs suggestive of TBU and in the diagnostic tests (TST, QFT-G test and microbiological/molecular tests) conducted in the different studies.

Clinical outcome of TBU cases on ATT was measured in terms of resolution or improvement of inflammation after completion of treatment. Studies that reported clinical outcomes only in terms of visual outcomes were not selected because such assessment could be affected by non-inflammatory conditions such as cataracts, macular pathology, glaucoma and optic neuropathy.[42]

The clinical outcome in our systematic review and meta-analysis was 82.0%. This estimate is similar to an earlier systematic review published in 2016.[62] In addition to ATT, the use of ocular and/or systemic corticosteroids, to control inflammation, was mentioned in all the studies included in our systematic review and meta-analysis. The clinical outcome, stratified by the level of TB burden, showed an 88.0% and 79.0% clinical response for cases from TB HBCs and non-HBCs settings, respectively (Fig. 3); however, this was not significantly different. The overall heterogeneity for clinical outcomes was considerable. We attempted to address this by pooling the studies into HBCs and non-HBCs for TB, into the different number of ATT drugs, and into the different ATT durations. Despite this, the intragroup heterogeneity was 'considerable' in the different subgroups except for that in HBCs for TB (I^2 = 0.00%, P = 0.60). The heterogeneity being 'not important' in the HBC group may have been due to the consistent use of oral corticosteroids in addition to ATT in 5 out of the 6 studies.

Although we included studies that had clinical outcomes after the completion of ATT, there were no studies with long-term outcomes. The multicenter Collaborative Ocular Tuberculosis Study (COTS) Group reported a long-term clinical outcome of 77.0% at 24-month, [5] which is slightly lower than the overall response of 82.0% in our meta-analysis. The COTS

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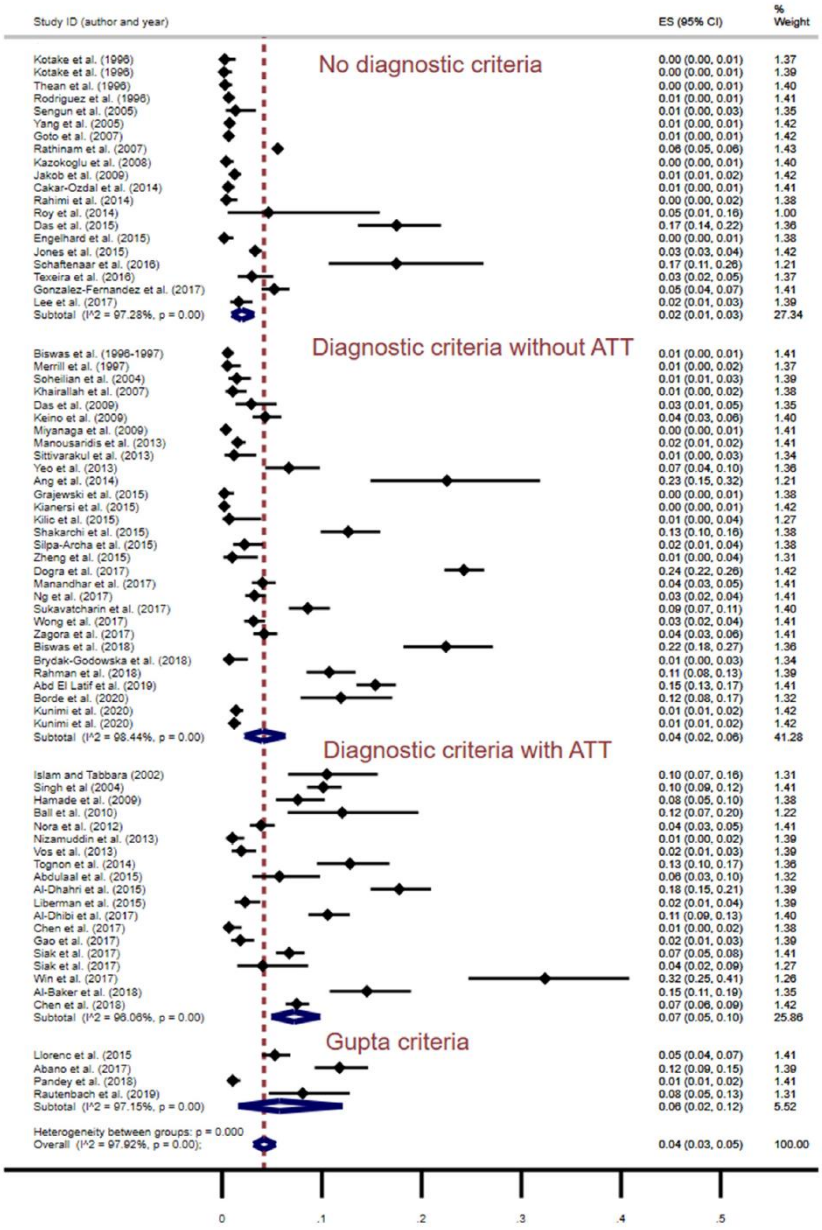


Fig. 6 – Meta-analysis of TB prevalence according to diagnostic criteria.
Gupta criteria: Diagnostic criteria according to Gupta et al review articles[53,55] but criteria not specified in the studies.

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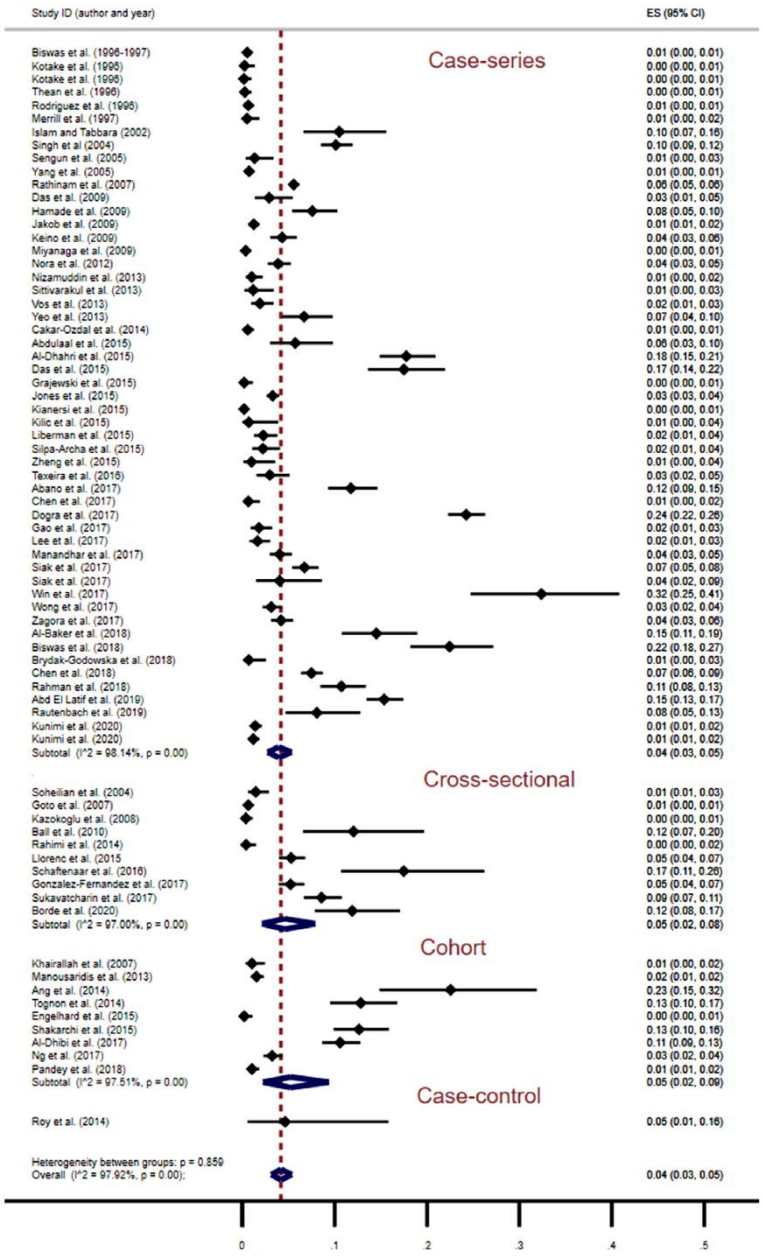


Fig. 7 – Meta-analysis of TB prevalence according to study design.

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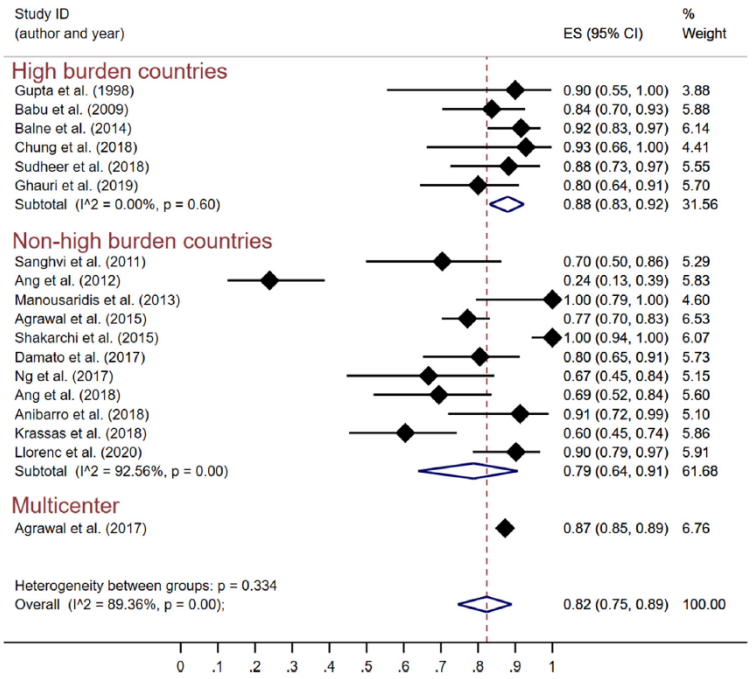


Fig. 8 – Meta-analysis of clinical outcome* studies stratified by HBCs and non-HBCs for TB.
***Clinical outcome defined as clinical (inflammatory) response to ATT.**

study group defined "cure" as TBU-inactivity 24 months after completing ATT. An earlier report of the same cohort, with a clinical response of 87.0%, is included in our meta-analysis.[6]

The systematic review by Kee and coworkers[62] did not report on the treatment outcomes in HBCs and non-HBCs, and did not compare different anti-TB drug regimens, in relation to the number of drugs and duration of treatment. Our analysis of the clinical outcome stratified by the number of drugs showed the pooled clinical outcome for studies with 3-drug (RHZ) ATT in the first 2 months was higher than that for 4-drug (RHZE) ATT (Fig. 8), but this difference was not significant; however, only 1 study reported on a 3-drug regimen (Fig. 8).[54]

In terms of ATT duration, studies that had treatment duration of 6 months compared to ≥9 months had higher clinical outcomes, but this difference was not statistically significant (Fig. 4). Ang and coworkers and Agrawal and coworkers reported that TB uveitis cases treated with ATT for ≥9 months duration had a lower rate of recurrence; whilst inclusion of corticosteroid had no effect on recurrence of inflammation.[7,14] Further studies are needed to elucidate the role of anti-TB drug regimen, especially the duration of treatment, on clinical outcome. The other factors that affect clinical outcome, specifically inflammatory outcome, that need to be considered are: (1) the different corticosteroid regimens used; (2) patient compliance in the different studies, (3) that the TBU might be an immune reaction against tubercular antigens / dormant *Mtb* bacilli and therefore ATT may be less effective in this subgroup of patients[44,46,116]; (4) that a misdiagnosis of TBU is a possibility, given the difficulty in making the diagnosis and; (5) that there might be resistance to ATT.[99]

Limitations to this systematic review and meta-analysis include the possibility of eligible articles being missed although we searched 3 different databases. Studies in all languages were included in the initial search, however, inaccessible published studies in a language other than English, may have been missed.

The stratification of prevalence according to HBCs and non-HBCs is a limitation in that it is not clear-cut; immigrants from TB-high-burden countries may have contributed to the prevalence of TBU in the non-HBC group. Another limitation is the arbitrary division of studies with data collection starting before 2010 and during or after 2010 based on the assumption that the diagnostic criteria defined by Gupta and coworkers would be widespread from 2010 onward.[55]

Limitations in interpreting the data included heterogeneity in the methodology; including lack of standardization in study design, demographic information, diagnostic criteria for TB uveitis (TBU), anti-TB drug regimen, duration of ATT and clinical outcome endpoints. There was also heterogeneity in data quality, the tool of which was adapted from the JBI assessment tool.[81,82]

The lack of demographic information meant that we were unable to accurately determine the mean age and male to female ratio, and we were unable to stratify prevalence accord-

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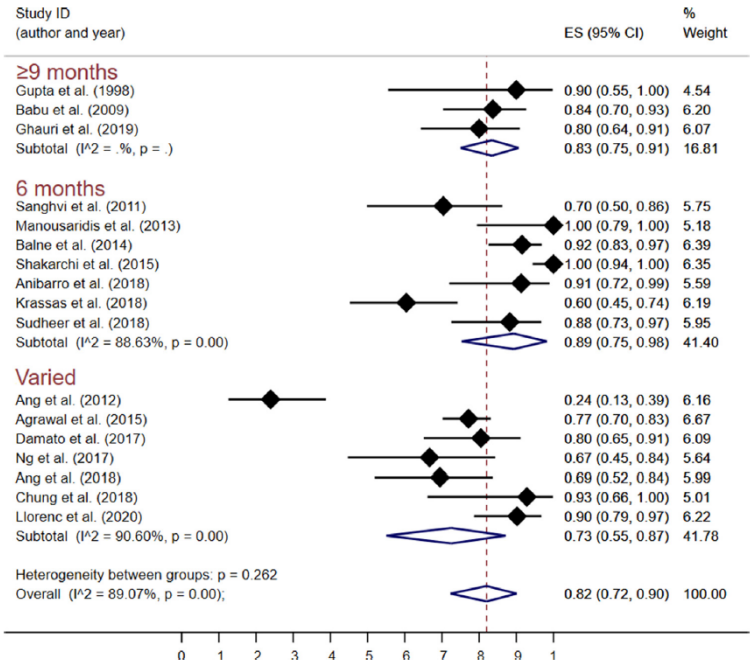


Fig. 9 – Meta-analysis of clinical outcome according to treatment duration.
Varied = studies in which ATT duration was <9 months in some patients and ≥9 months in others.

ing to age, gender, race, nationality and HIV status. Although comparisons were made across different diagnostic criteria, ATT regimen and treatment duration, there was still heterogeneity in these subgroups. Although we only included articles that had clinical outcomes on completion of ATT, we could not compare clinical outcome across set time frames because of the variation in clinical outcome endpoints.

5. Conclusion

Despite the limitations, our systematic review and meta-analysis is the first to estimate the global prevalence of TBU stratified by HBCs and non-HBCs and by different geographic regions. Additionally, it is the first to stratify clinical outcomes by HBCs and non-HBCs. Heterogeneity in the diagnosis and treatment of TBU indicates that future prospective cohort studies with standardized diagnostic criteria and treatment regimens for TBU are warranted.

6. Methods of literature search

6.1. *Search methods for identifying studies*

A literature search of PubMed, EMBASE and Scopus databases was last conducted on July 1, 2020 using the search terms detailed in Table 4. The search included English and other-language publications. However, full non-English publications that were not translated to English were excluded. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)[80] checklist and flow diagram were used to identify, screen and exclude studies (Fig. 1). A reference manager, Zotero, was used to import the titles of all the studies from the 3 databases. Duplicate titles were manually removed.

6.2. *Eligibility criteria for considering studies for this review*

All studies published before and until June 30, 2020 were included if they: (1) had ≥20 uveitis cases for prevalence estimates of TBU, or ≥ 5 uveitis cases for clinical outcomes; (2) described patients of all ages; (2) included all anatomical classification types (anterior, intermediate, posterior and panuveitis); (4) reported the prevalence of TBU in a population of uveitis cases, and for clinical outcomes, reported the response of inflammatory activity after completion of anti-TB treatment in TBU cases. Studies were excluded for description of TBU prevalence among uveitis cases if: (1) it exclusively assessed HIV positive or negative patients; (2) limited to a specific patient population and exclusion of others based on race or ethnicity; and (3) data were missing or did not correlate within the same publication. For clinical outcomes, studies were excluded if: (1) clinical (inflammatory) outcome to ATT

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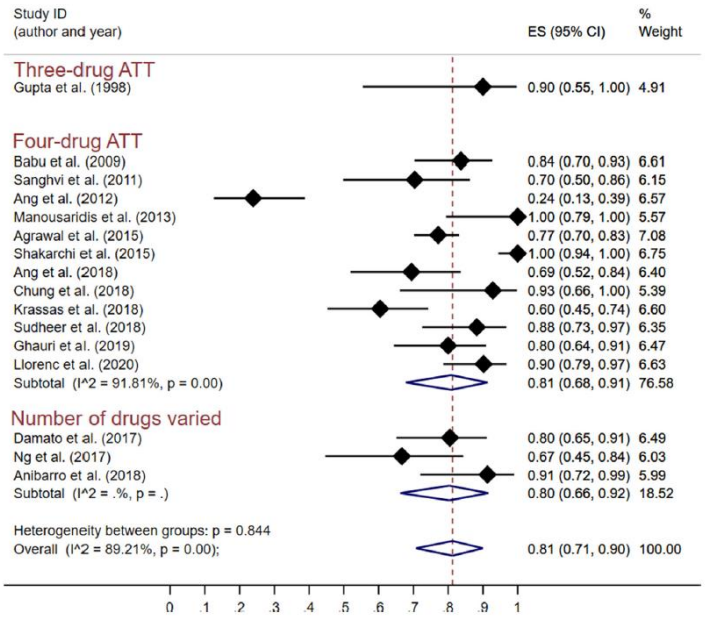


Fig. 10 – Meta-analysis of clinical outcome stratified by the number of anti-TB drugs.

Table 4 – Search strategy and terms.

	Tuberculosis AND Uveitis AND Diagnosis
OR	(("Diagnosis"[Mesh]) AND "Tuberculosis"[Mesh]) AND "Uveitis"[Mesh]
OR	Tuberculosis Uveitis AND Diagnosis
OR	Diagnosis of Tuberculous Uveitis
OR	TB Uveitis AND Diagnosis
OR	Diagnosis of TB Uveitis
OR	Tuberculosis AND Uveitis AND Treatment
OR	(("Tuberculosis" [MESH] AND "Uveitis" [MESH]) AND "Treatment outcome" [MESH]
OR	Tuberculous Uveitis AND Treatment Outcomes
OR	TB Uveitis AND Treatment Outcomes
OR	Tuberculosis AND Uveitis
OR	(("Tuberculosis"[MESH]) AND "Uveitis" [MESH]
OR	Tuberculous Uveitis
OR	TB Uveitis
OR	TB AND Uveitis
OR	Tuberculosis AND Ocular Inflammation
OR	Tuberculous Ocular Inflammation
OR	TB AND Ocular Inflammation'
OR	Tuberculous Uveitis AND Prevalence
OR	Tuberculous Uveitis AND Incidence

was part of the diagnostic criteria for TBU in the same study; and (2) data were missing or did not correlate within the same publication.

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Declaration of interest

None

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Appendix 2

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Article

Tubercular Uveitis in Uveitis Cases in a High TB and HIV Setting: A Prospective Cohort Study

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Purpose: The diagnosis of tubercular uveitis (TBU) is difficult. The lack of a diagnostic gold standard has contributed to challenges in determining the true prevalence and clinical predictors of TBU. We aimed to determine the proportion of TBU cases in adults with uveitis and to examine clinical features associated with TBU.

Methods: A prospective cohort study of adult uveitis cases after exclusion of other specific etiologies. The diagnosis of TBU was based on a composite reference of: any clinical signs of uveitis; exclusion of other causes of uveitis; and positive QuantiFERON-Gold test, tuberculin skin test, and/or ocular TB polymerase chain reaction.

Results: Of 79 cases analyzed, 49 (62%) had TBU. Female sex ($P = 0.001$) and chronic uveitis ($P = 0.006$) cases were more common in the TBU group than the non-TBU group whereas diffuse choroiditis ($P = 0.010$) and HIV-positive ($P = 0.001$) cases were less common. Choroidal granulomas ($P = 0.176$) and serpiginous-like choroiditis ($P = 0.292$) were more common in TBU group, albeit not significantly. On univariate analysis, female sex (odds ratio, 5.1; $P = 0.002$), negative HIV status (odds ratio, 0.2; $P = 0.001$), and chronic uveitis (odds ratio, 4.1; $P = 0.008$) were associated with TBU. A negative HIV test was associated with TBU on multivariate analysis ($P = 0.049$).

Conclusions: A high proportion of cases had TBU. Our study did not significantly confirm some of the clinical features associated with TBU reported in other studies.

Translational Relevance: Our study highlights the difficulties in determining the proportion and clinical predictors of TBU, especially in the absence of a gold standard diagnostic test.

Introduction

Tuberculosis has varyingly been attributed to causing 0.2% to 32% of uveitis.[1,2] Tubercular uveitis (TBU) can present with clinical features involving different ocular structures,[3] including broad-based posterior synechiae, retinal vasculitis, optic neuropathy, and choroidopathies such as serpiginous-like choroiditis and choroidal granulomas.[4–8] It can result in ocular morbidity, such as visual impairment, chronic hypotony, and blindness.[9] Adverse visual sequalae after TBU are associated with a delay in diagnosis, chronic disease, and posterior uveitis with choroiditis.[9] Complications of visual impairment could be due to optic neuropathy, macular oedema, glaucoma, vitreous hemorrhage, cataract, and macular scarring.[9]

The diagnostic difficulties of TBU are due to the inherent problems with the diagnostic tests and obtaining the optimal ocular sample for testing. There is a

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low positive yield in microbiological or molecular tests of ocular fluids and a low sensitivity and specificity of adjunct immunological tests such as the tuberculin skin test (TST) or TB-specific IFN-γ release assays, such as the QuantiFERON-TB Gold (QFT-G).[10–13] Consequently, there is no standardized diagnostic criteria for the diagnosis of TBU.

Although Gupta et al[3,4] proposed the diagnosis of TBU being based on varying combinations of suggestive clinical features of TBU, laboratory investigations, exclusion of other causes of uveitis, and response to antitubercular treatment, a number of studies have based the diagnosis on QFT-G and/or TST and/or polymerase chain reaction (PCR) test in the presence of uveitis.[14–17] Studies have reported a higher prevalence (44% to 48%) of TB being associated with uveitis if the diagnosis is based on a positive QFT-G.[17,18]

We undertook a prospective cohort study to determine the proportion of TBU cases in adults with uveitis and to examine the associations of ocular clinical features with TBU.

Materials and Methods

We conducted a prospective cohort study of uveitis cases referred to the Uveitis Clinic at St John Eye Hospital between June 2014 and November 2018. St John Eye Hospital is the Ophthalmology Department of Chris Hani Baragwanath Academic Hospital based in Johannesburg, South Africa, and has the highest prevalence of HIV infection in the world.[19] It is a public tertiary care hospital with limited resources serving a low-income population. The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand (M130942) and followed the tenets of the Declaration of Helsinki. Informed consent was obtained from all participants in the study.

Participants were eligible for inclusion in the study if they had any clinical signs of uveitis and were more than 18 years of age. If the participant had bilateral uveitis, only one eye (the eye with worse visual acuity and inflammatory activity) was included for PCR testing and statistical analyses. Individuals were excluded if they (i) had a previous or concurrent TB infection, (ii) had traumatic uveitis or postsurgical uveitis, (iii) were clinically diagnosed uveitis such as acute retinal necrosis, progressive outer retinal necrosis, cytomegalovirus (CMV) retinitis, Behcet's disease, Vogt–Koyanagi–Harada disease, Fuchs heterochromic iridocyclitis, sympathetic ophthalmia, birdshot chorioretinopathy, multiple evanescent white dot syndrome, punctate inner choroidopathy, or acute posterior multifocal placoid pigment epitheliopathy, and (iv) had uveitis caused by toxoplasmosis, syphilis, systemic lupus erythematosus, or sarcoid on blood workup and chest radiography.

All individuals presenting to St John Eye Hospital underwent a standard screening protocol for uveitis that included slit-lamp examination and fundoscopy, and investigations including full blood count and differential, erythrocyte sedimentation rate, HIV, $CD4^+$ lymphocyte count if HIV-positive, rapid plasma reagin and *Treponema pallidum* hemagglutination assay, serum angiotensin converting enzyme levels, *Toxoplasma* antibodies, antinuclear antibodies, antineutrophil cytoplasmic antibodies, and a chest radiograph to exclude other causes of uveitis. Furthermore, we did tuberculin skin testing using the Mantoux method (0.1 mL containing 2TU RT 23 [Statens Serum Institute, Copenhagen, Denmark] injected intradermally) and QuantiFERON-TB Gold (QFT-G [Cellestis Limited, Carnegie, Victoria, Australia]). Also, ocular fluids (aqueous or vitreous samples) were referred to the National TB Reference Laboratory and tested by TB PCR (Xpert MTB/RIF [Cepheid, Sunnyvale, CA], in-house MPB 64 PCR and in-house IS6110 PCR) and a viral panel PCR (varicella-zoster virus [VZV], herpes simplex virus [1 and 2], CMV, Epstein–Barr virus, and human herpes virus 6). Optical coherence tomography, fluorescein angiography, and lumbar puncture were performed depending on the clinical examination and blood results.

A diagnosis of TBU was made using a composite reference that included (i) any clinical signs of uveitis, (ii) other causes of uveitis were excluded, and (iii) QFT-G, and/or TST, and/or TB PCR of aqueous or vitreous samples were positive. Participants with a positive QFT-G and/or TST were diagnosed with presumed TBU and with positive PCR for TB with confirmed TBU. A TST of 10 mm or more at 48 hours after intradermal injection was considered positive in HIV-negative cases, and a TST of more than 5 mm was considered positive in HIV-positive cases. A QFT-G of 0.35 IU/mL or more was considered positive as per the manufacturer's recommendations. The QFT-G was performed before the TST. Indeterminate QFT-G results were correlated with the TST and the TB-PCR test; if the TST and/or TB-PCR test was positive, the participant was diagnosed with TBU and if these tests were negative, the participant was diagnosed with non-TBU.

All diagnosed TBU cases were treated with antitubercular treatment for 9 months: Rifafour e-275 (rifampicin [R] 150 mg, isoniazid [H] 75 mg, pyrazinamide [Z] 400 mg, and ethambutol hydrochloride [E] 275 mg) for the first 2 months,

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and RIFINAH-150 (rifampicin 150 mg and isoniazid 100 mg) or RIFINAH-300 (rifampicin 300 mg and isoniazid 150 mg) for 7 months; the dose was weight dependent. If necessary, and depending on the severity of inflammation, TBU cases were additionally treated with topical and/or oral corticosteroids. TBU cases were followed for a further 6 months after completion of antitubercular treatment, totaling 15 months of follow-up. All non-TBU cases were treated with topical steroids and/or systemic corticosteroid and/or immunosuppressive medication and, also followed-up for 15 months. All cases (TBU and non-TBU) were assessed for intraocular inflammation every 6 to 12 weeks for 15 months. Remission was defined as no inflammatory activity and being on 10 mg or less oral prednisone[20] for 6 months duration after the completion of 9 months treatment.

Demographic and clinical characteristics were documented in the TBU- and non-TBU groups. Characteristics that were documented and compared included age, gender, HIV status, laterality (unilateral vs. bilateral), TB contact, Bacillus Calmette-Guerin vaccination at birth, clinical course of uveitis, anatomical classification, type of choroiditis, clinical signs suggestive of TBU,[4–8] and remission of uveitis. Uveitis was anatomically classified as anterior, intermediate, posterior or panuveitis according to the Standardization of Uveitis Nomenclature criteria.[20] The clinical course of the uveitis (acute, recurrent, or chronic) and grading of intraocular inflammation was according to the Standardization of Uveitis Nomenclature criteria.[20] The clinical signs suggestive of TBU, from previous studies,[4–8] that were documented and evaluated were broad-based posterior synechiae, vasculitis, optic neuropathy, choroidal granulomas, and serpiginous-like choroiditis. A choroidal granuloma (large) was defined as a solitary mass of more than 4 mm; multifocal choroiditis as multiple discrete lesions (each ≤4 mm) or multiple discrete areas of inflammation; and serpiginous-like choroiditis as choroidal lesions that start around the disc and spreading centrifugally that are initially noncontiguous and eventually becoming confluent.[3] Diffuse choroiditis was defined as nondiscrete diffuse inflammation of the choroid.

Statistical Analysis

Continuous variables were summarized as means (standard deviation) if normally distributed or medians (interquartile range) if they were skewed. The comparison of means between the TBU and non-TBU groups was performed using the two-sample *t*-test. The comparison of medians between the two groups was performed using the Wilcoxon rank-sum test. A χ^2 or Fisher's exact test was used to compare categorical variables. Univariate logistic regression was used to evaluate the diagnosis of TBU as the outcome with the predictor variables of age, gender, HIV, laterality, TB contacts, Bacillus Calmette-Guerin vaccination at birth, chronicity of uveitis, and clinical signs such as broad-based synechiae, vasculitis, optic neuropathy, serpiginous-like choroiditis, and choroidal granulomas. The selection of variables in the multivariate logistic regression analysis was done by a stepwise regression method using backward elimination, with significance levels of 0.2 or less for inclusion. The estimate of odds ratio (OR) and its relative 95% confidence interval (CI) were calculated. The models were assessed using receiver operating characteristics curves. All analyses were performed using STATA version 16.1 (StataCorp LLC, College Station, TX). For all tests, a *P* value of less than 0.05 was considered statistically significant.

Results

Forty-nine (62%) of the enrolled 79 cases were diagnosed with TBU, including 41 with presumed TBU and 8 with confirmed TBU (Table 1). Of the 30 non-TBU cases, three were positive for VZV on ocular fluid PCR testing. The three cases with VZV infection had no ocular signs suggestive of acute retinal necrosis, progressive outer retinal necrosis, or CMV at study entry. Additionally, a further four of the 30 non-TBU cases were positive for Epstein–Barr virus on ocular fluid PCR testing. The overall and TBU cases mean age were 40.1 ± 12.2 and 41.8 ± 13.4 years, respectively (Table 1). Twenty-five of the 79 patients (32%) were males, albeit there being a lower percentage (18% [9/49]) among the TBU cases. Thirty cases (38%) were living with HIV, including 24% in those with TBU (Table 1). The median $CD4^+$ cell count of the HIV-positive cases in the TBU group was 233 (interquartile range, 155–473) and the non-TBU group 137 (interquartile range, 105–278). Forty-three (54%), 39 (50%), and 8 (10%) cases had a positive TST, QFT-G, and TB PCR, respectively (Table 2); one case with a positive QFT-G was classified as non-TBU because of a positive VZV PCR test. Forty-nine (62%) cases had at least one positive TB test.

Chronicity of uveitis (Table 2) was more common in TBU (73%) than non-TBU cases (42%) ($P = 0.006$). Ninety-six percent and 94% of TBU and non-TBU cases had panuveitis ($P = 0.632$), respectively (Table 2). The presence of diffuse choroiditis was lower in the TBU (6%) than non-TBU (27%) group ($P = 0.010$) (Table 2). The prevalence of broad-based posterior

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Table 1. Baseline Characteristics of TBU and Nontubercular Uveitis (Non-TBU) Cases

	Total	TBU	Non-TBU	*P* Value
No. (%)	**79 (100%)**	**49 (62%)** Presumed: 41 (84%) Confirmed: 8 (16%)	**30 (38%)**	
Age (years)	40.1 ± 12.2	41.8 ± 13.4	37.5 ± 9.7	0.135[a]
Male sex	25 (32)	9 (18)	16 (53)	**0.001**[b]
HIV positive ($n = 78$)	30 (38)	12 (24)	18 (62)	**0.001**[b]
$CD4^+$ cell count/L in HIV-positive cases ($n = 28$)	171 (121–294)	233 (155–473)	137 (105–278)	0.078[c]
Laterality				0.670[b]
Unilateral	19 (24)	11 (22)	8 (27)	
Bilateral	60 (76)	38 (78)	22 (73)	
Analyzed eye				
Right	37 (47)	17 (35)	20 (67)	
Left	42 (53)	32 (65)	10 (33)	
Anterior chamber/vitreous tap				
Anterior chamber	43 (54)	28 (57)	15 (50)	
Vitreous	36 (46)	21 (43)	15 (50)	
TB contact	14 (18)	7 (14)	7 (23)	0.307[b]
BCG vaccination at birth ($n = 78$)	66 (85)	40 (83)	26 (87)	0.691[b]

[a]Two-sample *t* test.
[b]χ^2 test.
[c]Wilcoxon rank-sum test. Values are number (%), mean ± standard deviation, or median (interquartile range). Boldface entries indicate statistical significance. BCG, Bacille Calmette-Guerin

synechiae ($P = 0.928$), vasculitis ($P = 0.352$), and optic neuropathy ($P = 0.151$) was not significantly different between the two groups. The prevalence of choroidal granulomas (13% vs. 3%; $P = 0.176$) and serpiginous-like choroiditis (8% vs. 0%; $P = 0.292$) was higher in the TBU group than the non-TBU group, although the difference was not significant. The proportion of cases in remission for 6 months duration after completing 9 months treatment (Table 2) was higher in TBU (43%) than non-TBU groups (18%), although it was not a significant difference ($P = 0.073$).

On univariate regression analysis (Table 3), the odds of TBU were higher in female cases (OR, 5.08; 95% CI, 1.83–14.06; $P = 0.002$) and cases with chronic uveitis (OR, 4.08; 95% CI, 1.44–11.59; $P = 0.008$), but lower in cases living with HIV (OR, 0.19; 95% CI, 0.07–0,54; $P = 0.001$). The multivariate logistic regression model was most predictive for the outcome when the following variables were included in the analysis: gender, HIV, chronic uveitis, and diffuse choroiditis (χ^2 goodness-of-fit test $P = 0.373$; area under the receiver operating characteristics curve, 0.803) (Table 4 and Fig.). A negative HIV test significantly predicted a diagnosis of TBU on multivariate analysis (OR, 0.313; 95% CI, 0.099–0.994; $P = 0.049$).

Discussion

The proportion of TBU cases in our study was 62%. The reported prevalence of TBU in several studies from high TB-burden countries range from 22% to 48%[1,17,21–24] and from non-high TB-burden countries range from 7% to 44%.[18,25] Although we report a higher proportion of TBU cases, direct comparison of our data with these studies is not possible because the prevalence of TBU reported in these studies is in a uveitis population that included cases with other etiologies. Our study excluded uveitis cases that had a specific etiology, such as acute retinal necrosis, progressive outer retinal necrosis, CMV retinitis, Behcet's disease, Vogt–Koyanagi–Harada disease, Fuchs heterochromic iridocyclitis, sympathetic ophthalmia, birdshot chorioretinopathy, multiple evanescent white dot syndrome, acute posterior multifocal placoid pigment epitheliopathy, punctate inner choroidopathy toxoplasmosis, syphilis, systemic lupus erythematosus, and sarcoid. The other reason for the high proportion of TBU cases in our study is that the diagnosis of TBU was based on a composite reference, including any of the following three positive tests—QFT-G, TST, and/or PCR. If a single test alone was used to make the

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Table 2. Clinical Characteristics of TBU and Nontubercular Uveitis (Non-TBU)

	Total	TBU	Non-TBU	*P* Value
No. (%)	79 (100)	49 (62) Presumed: 41 (84) Confirmed: 8 (16)	30 (38)	
Anatomical classification				
Anterior	1 (1)	1 (2)	0 (0)	
Intermediate	2 (3)	1 (2)	1 (3)	
Posterior	1 (1)	0 (0)	1 (3)	
Panuveitis	75 (95)	47 (96)	28 (94)	0.632[a]
Course of uveitis ($n = 77$)				
Acute	24 (32)	10 (21)	14 (48)	
Chronic	47 (61)	35 (73)	12 (42)	**0.006**[b]
Recurrent	6 (7)	3 (6)	3 (10)	
Fundus pathology				
Choroiditis type				
Multifocal (multiple lesions, each <4 mm)	52 (66)	34 (69)	18 (60)	0.393[b]
Serpiginous-like	4 (5)	4 (8)	0 (0)	0.292[a]
Diffuse	11 (14)	3 (6)	8 (27)	**0.010**[b]
Granulomas (≥4 mm)	7 (9)	6 (13)	1 (3)	0.176[b]
Vasculitis only	2 (2)	0 (0)	2 (7)	
No fundus lesions	3[c] (4)	2 (4)	1 (3)	
Clinical signs[5–8,d] suggestive of intraocular tuberculosis				
Broad-based posterior synechiae	18 (23)	11 (22)	7 (23)	0.928[b]
Vasculitis	39 (50)	22 (46)	17 (57)	0.352[b]
Optic neuropathy	4 (5)	1 (2)	3 (10)	0.151[a]
Choroidal granulomas	7 (12)	6 (13)	1 (3)	0.176[b]
Serpiginous-like choroiditis	4 (5)	4 (8)	0 (0)	0.292[a]
Remission for 6 months duration after completing ATT (TBU, $n = 35$) or completing anti-inflammatory medication (non-TBU, $n = 17$)				0.073[b]
Yes	18 (35)	15 (43)	3 (18)	
No	34 (65)	20 (57)	14 (82)	
Positive TST	43 (54)	43 (88)	0 (0)	
Quantiferon-TB Gold ($n = 78$)				
Positive	39 (50)	38 (79)	1[e] (3)	
Mtb PCR ($n = 78$)				
Negative	67 (86)	38 (79)	29 (97)	
Indeterminate[f]	3 (4)	2 (4)	1 (3)	
Positive	8 (10)	8 (17)	0 (0)	
Viral PCR ($n = 78$)				
Varicella zoster virus	3 (4)	0 (0)	3 (10)	
Epstein-Barr virus	5 (6)	1 (2)	4 (13)	
Negative	70 (90)	47 (98)	23 (77)	

[a]Fishers exact test.
[b]χ^2 test.
[c]Three cases had no fundus lesions; one had anterior uveitis and two intermediate uveitis.
[d]References of studies suggestive of clinical signs of intraocular tuberculosis.
[e]One case with a positive QuantiFERON test was classified as non-TBU because of a positive PCR for VZV.
[f]Cycle threshold >35 cycles. Values are number (%). Boldface entries indicate statistical significance. ATT, antituberculosis treatment; *Mtb*, *Mycobacterium tuberculosis* detected by IS6110 and MPB64 [none detected by Gene Xpert]); PCR, polymerase chain reaction.

diagnosis, the prevalence would have been lower. For example, the QFT-G positivity rate in our study was 50%. In high TB-burden countries the QFT-G positivity rate in all uveitis cases is reported at between 36% and 48%.[17,26] Gineys et al.,[18] from a low TB-burden country, reported a QFT-G positivity of 44% and proposed the treatment of TBU based on a positive QFT-G and TST. As mentioned elsewhere in this article, the greater proportion of patients with TBU may be due to an overestimation of the prevalence of TBU. Alternatively, it may reflect an accurately high proportion of TBU as evidenced by the higher proportion of TBU cases in remission for the duration of 6 months after completing antitubercular treatment

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Table 3. Univariate Logistic Regression of Variables Predicting TBU

Variable	OR	95% CI	*P* Value
Age	1.031	0.990–1.074	0.138
Gender (female)	5.079	1.834–14.064	**0.002**
HIV positive	0.198	0.073–0.535	**0.001**
Laterality (bilateral)	1.256	0.439–3.594	0.671
TB contacts	0.548	0.171–1.755	0.311
BCG received at birth	0.769	0.210–2.816	0.692
Course of uveitis			
Acute (reference group)	1.0		
Chronic	4.083	1.438–11.590	**0.008**
Recurrent	1.400	0.233–8.421	0.713
Choroiditis type			
Multifocal	1.511	0.584–3.908	0.394
Serpiginous	1		
Diffuse	0.564	0.351–0.906	**0.018**
Choroidal granulomas	4.047	0.463–35.396	0.206
Clinical signs[5–8,a] suggestive of intraocular tuberculosis			
Broad-based posterior synechiae	0.951	0.323–2.800	0.928
Vasculitis	0.647	0.258–1.621	0.353
Optic neuropathy	0.188	0.019–1.892	0.156
Choroidal granulomas	4.047	0.463–35.396	0.206
Serpiginous-like choroiditis	1		

Boldface entries indicate statistical significance.
[a]References of studies suggestive of clinical signs of intraocular tuberculosis.

Table 4. Multivariate Logistic Regression Model for Variables Predicting TBU[a]

Variable	OR	95% CI	*P* Value
HIV	0.313	0.099–0.994	0.049
Gender (female)	2.831	0.859–9.325	0.087
Chronic uveitis	1.483	0.844–2.608	0.171
Diffuse choroiditis	0.630	0.372–1.067	0.086

[a]$n = 76$, χ^2 goodness-of-fit test $P = 0.373$, area under the receiver operating characteristics curve = 0.803).

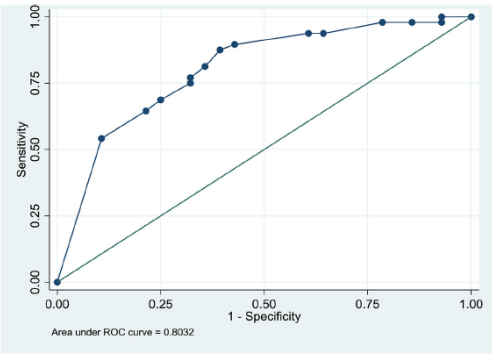


Figure. Receiver operating characteristics (ROC) curve of the multivariate regression model predicting TBU.

compared to non-TBU cases (43% vs. 18%). The difference was, however, not significant and a larger sample size may have shown significance between the two groups.

There was a significantly greater proportion of females and HIV-negative cases in the TBU group. These findings were similar to the study by Smit et al.,[24] which was also conducted in South Africa. Although several studies[27–29] have shown that females were strongly associated with extrapulmonary TB, some studies[16,24,30] on TBU showed a female preponderance, whereas others[14,31] (including the Collaborative Ocular Tuberculosis Study [COTS]-1) did not. This gender effect in extrapulmonary TB is thought to be related to access to health care, socioeconomic, and hormonal factors.[28,29] Although on univariate analysis female gender was significantly associated with TBU, this significance was lost in the multivariate analysis. There was a significantly higher proportion of HIV-negative cases in the TBU group. Because the diagnosis

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of TBU in most cases was based on a positive QFT-G or TST, a lower proportion of TBU cases being HIV positive may be due to higher false negative TB tests secondary to immunosuppression. This finding is supported by the lower median $CD4^+$ cell count in the non-TBU group. Because the sensitivity of these immunological tests is decreased in immunosuppressed individuals,[12,32] the diagnosis of TBU could have been underestimated in the HIV-positive cases. The T-spot.TB (Oxford Immunotech, Oxford, UK) test is more sensitive in diagnosing TB in HIV-positive individuals with lower $CD4^+$ cell counts[33] and might have yielded more TBU cases in our study; however, it is not available at our hospital. A study from Cape Town in South Africa also found a higher proportion of HIV negative cases diagnosed with possible intraocular TB[24]; the QFT-G test was used to support the diagnosis. In our study, a negative HIV test was significantly associated with TBU on both univariate and multivariate analyses.

The most common anatomic diagnosis in the TBU and non-TBU groups was panuveitis. The high prevalence of panuveitis reflects the referral pattern in our hospital; most anterior and intermediate uveitis cases are treated in the outpatient area and rarely referred to our uveitis clinic. TBU predominantly manifested as panuveitis in several studies.[16,18,34] In the COTS study, the most common anatomic presentation was posterior uveitis followed by panuveitis.[31] There was a significantly greater proportion of cases with chronic uveitis in the TBU group compared with the non-TBU group. If there was selection bias in that only chronic cases who did not respond to immunosuppressive treatment were referred, then this difference would have been reflected in both the TBU and non-TBU groups. Chronic uveitis was associated significantly with TBU on univariate analysis, but not on multivariate analysis.

Choroidal granulomas and serpiginous-like choroiditis are commonly associated with TBU.[5,8,35] In our study, there was a greater proportion of cases with choroidal granulomas and serpiginous-like choroiditis in the TBU group than in the non-TBU group; however, the difference was not significant and this lack may possibly be due to the small sample of cases with these signs. Diffuse choroiditis was significantly associated with non-TBU on univariate analysis, but not on multivariate analysis.

Broad-based posterior synechiae, retinal vasculitis and optic neuropathy are signs reportedly associated with TBU.[4,5] In our study, there was no significant difference of these signs between the TBU group and the non-TBU group. The reason for this may be due to the small number of cases with these clinical signs.

The limitations of our study include the limited number of cases in the subgroups, selection bias, and, as with all studies on TBU, the lack of a gold standard for the diagnosis of TBU. The limited number of cases in the clinical subgroups meant that, although differences in clinical signs were found between the TBU and non-TBU groups, statistical significance may not have been attained because of this. Selection bias may have contributed to the high proportion of TBU and the high proportion of panuveitis. The exclusion of uveitis cases with other etiologies probably resulted in a higher proportion of TBU, and the possible frequent referral of cases with panuveitis may have resulted in a higher proportion of these cases. The lack of a gold standard for the diagnosis of TBU and the reliance mainly on QFT-G and/or TST for its diagnosis may have contributed to the high proportion of TBU cases. Also, the lack of a gold standard makes the determination of the predictors difficult. However, it is because of this diagnostic difficulty we were looking for clinical predictors for the diagnosis of TBU. The strengths of the study include it being a prospective cohort study with a comprehensive ophthalmic and investigative evaluation, including QFT-G, TST, and TB PCR.

In conclusion, because of the inherent problems in the diagnostic tests for TBU, including in persons living with HIV, the true prevalence of TBU is difficult to determine. However, based on the higher remissions achieved in the TBU cases, we found these tests, especially QFT-G and TST, to be useful in the diagnosis of TBU. TBU was associated with a chronic course and HIV-negative cases. In terms of the other clinical predictors of TBU, we could not significantly confirm the clinical features associated with TBU reported in other studies because of the limited number of cases in the clinical subgroups. Thus, there is a need for a large multicenter prospective cohort study to determine the clinical predictors of TBU.

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Appendix 3

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ORIGINAL RESEARCH

Treatment Outcome of Tubercular Uveitis in a High TB and HIV Setting: A Prospective Cohort Study

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Purpose: To determine the time to resolution of inflammation in tubercular uveitis (TBU) cases on standard anti-tubercular treatment. Sub-analysis of time to resolution according to HIV status was also performed.

Patients and Methods: A prospective cohort study of presumed idiopathic uveitis cases >18 years underwent the tuberculin skin test, QuantiFERON-TB Gold test, and ocular tuberculosis (TB) polymerase chain reaction test. Adult TBU cases were treated with standard anti-tubercular therapy (and corticosteroids) for 9 months. Cases were followed-up for resolution of inflammation at 1.5, 3, 6, 9, 12 and 15 months post-diagnosis. Outcome measure was resolution of inflammation on ≤10 mg oral prednisone per day.

Results: Seventy-nine presumed idiopathic uveitis cases were enrolled in the study, 49 (62%) were diagnosed with TBU. The mean (SD) age of TBU cases at diagnosis was 41.8 (13.4) years. Using a multilevel mixed effects model, resolution was achieved at 6 months in the TBU cases (OR = 1.21; 95% CI, 1.03–1.41; $P = 0.017$). Using generalized estimating equations, resolution was also achieved at 6 months in the TBU cases (OR = 1.21; 95% CI, 1.05–1.39; $P = 0.008$). The HIV-positive cases (OR = 1.62; 95% CI, 1.13–2.31; $P = 0.008$) and the HIV-negative cases (OR = 1.25; 95% CI, 1.06–1.48; $P = 0.009$) achieved resolution at 9 months.

Conclusion: Resolution of inflammation in TBU cases on anti-tubercular treatment with corticosteroids was achieved at 6 months and maintained throughout the study. Our study suggests a minimum of 6 months treatment is required for significant resolution. Resolution of inflammation in HIV-positive and HIV-negative TBU cases needs to be further explored.

Keywords: *Mycobacterium tuberculosis*, anti-tubercular treatment, inflammation, HIV, resolution

Introduction

Tubercular uveitis (TBU) is defined as intraocular inflammation secondary to *Mycobacterium tuberculosis* infection.[1] There is no gold standard for its diagnosis, and therefore the diagnosis of TBU is challenging.[2] Tubercular uveitis is defined as definite if the microbiological/molecular tests of intraocular fluid are positive. However, the poor positivity rate (37.7 – 58.8%) of these tests has resulted in the diagnosis of TBU in most cases being mainly presumptive.[3–5] A diagnosis of presumed TBU, following exclusion of other causes of uveitis, is often based on a combination of clinical signs of uveitis, tuberculin skin test (TST) or interferon-gamma release assay (IGRA) reactivity, chest radiography and/or non-ocular micro-biological/molecular tests, and/or a positive response to anti-tubercular treatment.[2,6]

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Treatment outcomes of TBU vary; this is partly due to the misdiagnosis of TBU, resistance to anti-tubercular treatment, variation in anti-tubercular treatment regimen (including treatment duration), and the variation in the concomitant corticosteroid-use to control inflammation.[7] Good recovery rates on anti-tubercular treatment with corticosteroids have been reported in individuals with presumed (93–100%)[8–10] and definite (90–92%)[3,11] TBU. However, lower recovery rates (24% to 67%) in presumed TBU cases have been reported.[12–14] The Collaborative Ocular Tuberculosis Study (COTS) reported a recovery rate of 87.0% in presumed TBU cases 6 months after completing anti-tubercular treatment.[15] A follow-up of the same cohort of cases yielded a long-term recovery rate of 77.0% at 2 years.[16] A meta-analysis of treatment outcomes reported an overall global recovery rate of 82% in TBU cases after completing anti-tubercular treatment.[7]

The optimal duration of anti-tubercular treatment yielding a good treatment response with minimal risk of adverse events has been debated. Alvarez et al and Vos et al mentioned that treatment for presumed TBU should be stopped in cases responding poorly after 2–4 months of anti-tubercular treatment.[17,18] However, this may be too early to consider terminating treatment as other studies have reported poor treatment outcomes in cases treated for a shorter duration.[12,19] Cases receiving anti-tubercular treatment and concomitant corticosteroids for 3 months had a lower recovery rate (50%) than cases treated for 9 months or longer (77%).[19] A longitudinal study assessing recurrence rates in TBU cases treated with concomitant anti-tubercular treatment and corticosteroids for at least 12 months reported a low recurrence rate (16%).[20] Another longitudinal study reported a recurrence rate of 30% in TBU cases treated with a similar regimen for 6 months.[21]

Although studies seem to suggest that a shorter anti-tubercular treatment duration for TBU is inadequate for a good outcome, longitudinal studies assessing the minimum treatment duration needed to achieve significant resolution are sparse. We, therefore, performed a prospective cohort study to determine the timeframe when significant resolution of inflammation in TBU cases on standard anti-tubercular treatment for 9 months occurs, and the duration of time resolution is maintained. Additionally, we sub-analyzed the timeframe for resolution according to HIV status.

Materials and Methods

We undertook a prospective, descriptive cohort study of individuals referred to the uveitis clinic at St John Eye Hospital from 2014 until 2018. St John Eye Hospital is a tertiary hospital in Johannesburg, South Africa, a country which is endemic for TB and which has the highest prevalence of human immunodeficiency virus (HIV) infection in the world.[22,23] Individuals were included in the study if they, i. had active uveitis, ii. were ≥18 years of age, iii. had no prior or concurrent pulmonary or other extrapulmonary TB, and iv. had no previous anti-tubercular treatment. Excluded from the study were individuals that had: i. traumatic uveitis or post-surgical uveitis; ii. clinically diagnosed uveitis such as acute retinal necrosis (ARN), progressive outer retinal necrosis (PORN), cytomegalovirus (CMV) retinitis, Behcet's disease, Vogt-Koyanagi-Harada (VKH) disease, Fuchs heterochromic iridocyclitis (FHI), sympathetic ophthalmia, HLA-B27-associated acute anterior uveitis (AAU), birdshot chorioretinopathy, multiple evanescent white dot syndrome (MEWDS), punctate inner choroidopathy (PIC) and acute posterior multifocal placoid pigment epitheliopathy (APMPPE); and iii. uveitis caused by toxoplasmosis, syphilis, systemic lupus erythematosus (SLE) and sarcoid on blood workup and chest radiography. Uveitis was defined as "presumed idiopathic" in participants included in the study, if no cause was found on clinical examination, blood workup and chest radiography.

The investigative work-up to exclude other causes of uveitis before study entry were 1. chest radiograph; and 2. laboratory evaluation, such as full blood count (FBC) and differential, erythrocyte sedimentation rate (ESR), human immunodeficiency virus (HIV) ELISA, CD4+ lymphocyte count if HIV-positive, rapid plasma reagin (RPR) and *Treponema pallidum* hemagglutination assay (TPHA), serum angiotensin converting enzyme (sACE) levels, *Toxoplasma* antibodies, antinuclear antibodies (ANA) and antineutrophil cytoplasmic antibodies (ANCA). We performed an ophthalmological assessment and investigative evaluation on all included participants which included 1. anterior and posterior segment examination; 2. Tuberculin skin test (Mantoux method [Statens Serum Institute, Copenhagen, Denmark])), QuantiFERON-TB Gold test (QFT-G [Cellestis Limited, Carnegie, Victoria, Australia]), and anterior chamber or vitreous tap which was sent for PCR to identify MTB (Xpert MTB/RIF [Cepheid, Sunnyvale, CA], in-house MPB 64 PCR and in-house IS6110 PCR). Participants presenting with bilateral uveitis had ocular fluid from one eye (the eye with the worse visual acuity and inflammatory activity) sampled for PCR testing. Based on the results of the investigative

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evaluation, TBU cases were identified from the cohort of presumed idiopathic uveitis cases.

We diagnosed TBU as follows: i. Confirmed or definite TBU if TB PCR was positive and possible or presumed TBU if TST and/or QFT-G were positive in the presence of uveitis; and ii. All other causes of uveitis were excluded. A TST ≥ 10 mm induration 48 hours after intradermal injection in HIV-negative patients was considered positive for TBU, and in HIV-positive patients ≥5mm.[24] The TB antigen value minus the negative control value ≥0.35 IU/mL in the QFT-G test was considered positive for TBU. The TST was performed after the QFT test. The IS6110 and MPB64 gene sequence of *Mycobacterium tuberculosis* were the targets used for PCR.

All cases diagnosed with TBU were treated with fixed dose combination anti-tubercular treatment. Rifafour e-275 (Rifampicin [R] 150 mg, Isoniazid [H] 75 mg, Pyrazinamide [Z] 400 mg, and ethambutol hydrochloride [E] 275 mg) was prescribed for the first 2 months, and RIFINAH-150 (Rifampicin 150 mg and Isoniazid 100 mg) or RIFINAH-300 (Rifampicin 300 mg and Isoniazid 150 mg) for the remaining 7 months. The total duration of anti-tubercular treatment was 9 months, and the dose was weight dependent. To control the inflammatory activity, TBU cases were additionally treated with corticosteroids during and after completion of anti-tubercular treatment. Topical corticosteroids were prescribed for TBU cases with anterior uveitis; oral and/or periocular corticosteroids for intermediate and posterior uveitis; and oral and/or topical and/or periocular corticosteroids for panuveitis. Periocular steroids were mainly advocated for cystoid macular oedema. Tubercular uveitis cases were followed up for a further 6 months after completion of anti-tubercular treatment, totaling 15 months follow-up.

We assessed all TBU cases for intraocular inflammation at 1.5, 3, 6, 9, 12 and 15 months post-diagnosis. At each follow-up visit, the grading and outcome of intraocular inflammation was according to the standardization of uveitis (SUN) criteria.[25] Resolution, which was the outcome measured during the study, was defined as no intraocular inflammation on ≤10 mg oral prednisone.[25] Remission was defined as no inflammatory activity and being on ≤10 mg oral prednisone for 6 months duration after completion of 9 months anti-tubercular treatment.[25] Participants who had bilateral uveitis were regarded as having achieved resolution or remission when they had no intraocular inflammation in both eyes.

The study was approved by the Human Research Ethics Committee (HREC) of the University of the Witwatersrand (M130942) and followed the tenets of the Declaration of Helsinki. Informed consent was obtained from all included participants prior to study entry.

Statistical Analysis

All data were collected and managed using the REDCap (Research Electronic Data Capture) tools hosted at the University of the Witwatersrand.[26,27] Data was analysed in Stata 16.1 (StataCorp, College Station, Texas). Continuous variables were summarized as means (standard deviations) if they were normally distributed and medians (interquartile range) if they were skewed. Missing data for the longitudinal analysis of resolution was addressed using multiple imputation with chained equations as the pattern of missingness was non-monotone. For the longitudinal analysis of resolution as the outcome across all visits we used a two-level multilevel mixed effects model as well as generalized estimating equations, the former to evaluate the individual-level response and the latter to evaluate the population-level response. An alpha-level of 0.05 was taken to be statistically significant.

Results

Seventy-nine presumed idiopathic uveitis cases were enrolled in the study; 49 (62%) were diagnosed with TBU of whom 41 (52%) cases were presumed TBU and 8 (10%) confirmed TBU (Table 1). The mean (SD) age of the TBU cases at diagnosis was 41.8 (13.4) years. Cases with TBU were more likely to be female (82%) and HIV-negative (76%), and to have chronic uveitis (73%) (Table 1). Ninety-six percent of the TBU anatomical classification type was panuveitis and 69% of cases had multifocal choroiditis (Table 1). Of the 49 TBU cases treated with anti-tubercular medication, concomitant oral corticosteroids were initiated in 46 (94%) cases, of which 43 cases were additionally treated with topical corticosteroids and six cases with periocular corticosteroids; one TBU case was treated with topical corticosteroids only (Table 1). Two TBU cases had no concomitant corticosteroid treatment. Thirty-five TBU cases (71%) completed study follow-up through to 15-months post-diagnosis, of whom 15 (43%) were in remission (Table 1).

Using a multilevel mixed effects model for the analysis of repeated outcomes at the individual level, the TBU cases achieved significant resolution at 6 months post-diagnosis (OR = 1.21; 95% CI, 1.03–1.41; P=0.017)

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Table 1 Baseline and Clinical Characteristics, and Treatment Outcomes of Tubercular Uveitis Cases

	TBU
N (%)	49 (62%)
Age (years)	
Mean (SD)	41.8 (13.4)
Gender	
Males	9 (18%)
Females	40 (82%)
HIV, n (%)	
Positive	12 (24%)
Negative	37 (76%)
Laterality, n (%)	
Unilateral	11 (22%)
Bilateral	38 (78%)
Anatomical classification[§], n (%)	
Anterior	1 (2%)
Intermediate	1 (2%)
Posterior	0 (0%)
Panuveitis	47 (96%)
Course of uveitis[§] (n = 48), n (%)	
Acute	10 (21%)
Chronic	35 (73%)
Recurrent	3 (6%)
Choroiditis type, n (%)	
Multifocal	34 (69%)
Serpiginous	4 (8%)
Diffuse	3 (6%)
Granulomas	6 (13%)
Nil	2 (4%)
Tuberculin skin test, n (%)	
Negative	6 (12%)
Positive	43 (88%)
Quantiferon-TB Gold (n = 48), n (%)	
Negative	10 (21%)
Positive	38 (79%)
TB PCR (n = 48), n (%)	
Negative	38 (79%)
Indeterminate	2 (4%)
Positive	8 (17%)
Viral PCR (n =48), n (%)	
VZV	0 (0%)
EBV	1 (2%)
Negative	47 (98%)
Concomitant corticosteroid treatment, n (%)	
Oral	46 (94%)
Topical	44 (90%)
Periocular	6 (12%)
Remission (n = 35), n (%)	
Yes	15 (43%)
No	20 (57%)

Note: [§]According to Standardization of Uveitis Nomenclature (SUN) criteria.
Abbreviations: TBU, tubercular uveitis; HIV, human immunodeficiency virus; TB, tuberculosis; PCR, polymerase chain reaction (*Mtb* detected by IS6110 and MPB64 [none detected by Gene Xpert]); VZV, varicella zoster virus; EBV, Epstein-Barr virus.

(Table 2). Resolution was maintained at subsequent visits (Table 2). This relationship was significant in both the univariate and multivariate models.

When using generalized estimating equations to assess the overall TBU population response (Table 3), the TBU population achieved significant resolution at 6 months post-diagnosis (OR = 1.21; 95% CI, 1.05–1.39; P=0.008). Again, using this method of analysis resolution was maintained at subsequent visits (Table 3). This

Table 2 Individual-Level Response Using Two-Level Multilevel Mixed Effects Model

TB Uveitis			
Univariate Multilevel Mixed Effects			
Predictor	**Odds Ratio**	***P*-value**	**95% CI**
Visit (months)			
1.5	1.02	0.78	0.88–1.19
3	1.10	0.209	0.95–1.29
6	1.21	0.017	1.03–1.41
9	1.33	0.001	1.13–1.56
12	1.50	<0.001	1.26–1.78
15	1.58	<0.001	1.34–1.85
Multivariate Multilevel Mixed Effects			
Predictor	**Odds Ratio**	***P*-value**	**95% CI**
Visit (months)			
1.5	1.02	0.777	0.88–1.19
3	1.10	0.203	0.95–1.29
6	1.20	0.016	1.03–1.41
9	1.33	<0.001	1.13–1.56
12	1.50	<0.001	1.26–1.78
15	1.58	<0.001	1.34–1.85
Age	1.00	0.74	1.00–1.004
Sex	0.85	0.009	0.75–0.96

Abbreviations: TB, tubercular; *P*, probability; CI, confidence interval.

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Table 3 Population-Level Response Using Generalized Estimating Equation

TB Uveitis			
Univariate Generalised Estimating Equations			
Predictor	**Odds Ratio**	***P*-value**	**95% CI**
Visit (months)			
1.5	1.02	0.757	0.89–1.17
3	1.10	0.163	0.96–1.27
6	1.21	0.008	1.05–1.39
9	1.33	<0.001	1.15–1.54
12	1.50	<0.001	1.28–1.76
15	1.58	<0.001	1.36–1.83
Multivariate Generalised Estimating Equations			
Predictor	**Odds Ratio**	***P*-value**	**95% CI**
Visit (months)			
1.5	1.02	0.757	0.89–1.17
3	1.10	0.163	0.96–1.27
6	1.21	0.008	1.05–1.39
9	1.33	<0.001	1.15–1.54
12	1.50	<0.001	1.28–1.76
15	1.58	<0.001	1.36–1.83
Age	1.00	0.809	0.996–1.01
Sex	0.85	0.053	0.72–1.00

Abbreviations: TB, tubercular; *P*, probability; CI, confidence interval.

association was maintained in both the univariate and multivariate analyses (Table 3).

A time-series plot, after multiple imputation, showed increasing number of TBU cases achieving resolution from 1.5 months through to 3-, 6-, 9-, 12-, and 15-months (Figure 1).

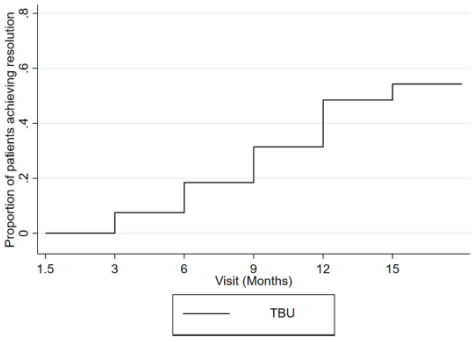


Figure 1 Proportion of tubercular uveitis (TBU) cases achieving resolution at follow-up visits.

Using a multilevel mixed effects model for the analysis of repeated outcomes, the HIV-positive cases (OR = 1.62; 95% CI, 1.13–2.31; *P*=0.008) and the HIV-negative cases (OR=1.25; 95% CI, 1.06–1.48; *P*=0.009) achieved significant resolution at 9 months post-diagnosis (Table 4).

Discussion

Our study provides a timeframe for when a significant proportion of TBU cases will achieve resolution, and suggests a minimum duration required for anti-tubercular treatment with corticosteroid medication to be effective.

Our study measured outcomes in terms of time to resolution of inflammation in TBU cases on 9 months anti-tubercular treatment and corticosteroids. In both the models used for analysis, the odds of resolution of inflammation increased in the follow-up visits and reached statistical significance at 6 months post-diagnosis of TBU. Also, resolution was subsequently significantly maintained throughout the study.

The resolution of inflammation at 6 months in our study suggests that the minimum duration of anti-tubercular treatment should be 6 months. However, since all the TBU cases in our study were treated for 9 months, we do not know if the same level of significance would have been maintained throughout the study if all participants had been treated with 6 months of anti-tubercular treatment. Although studies in which TBU cases treated for 6 months with anti-tubercular treatment reported good treatment outcomes,[7–9,11] Ang et al reported an eleven-fold decrease in the likelihood of recurrence of inflammation in TBU cases treated with anti-tubercular treatment for ≥ 9 months compared to cases treated < 9 months.[12] Anti-tubercular treatment is associated with significant adverse effects, including optic neuropathy, which can be minimized with a shorter duration of exposure to anti-tubercular treatment.[2] Therefore, it is important to determine if 6 months of anti-tubercular treatment will have the same effect as 9 months of anti-tubercular treatment. Large prospective cohort studies with longer follow-up comparing 6 months versus 9 months anti-tubercular treatment are needed to compare the length of time significant resolution can be maintained.

Our study also highlights the issue regarding the concomitant use of corticosteroids to control inflammation in TBU. Corticosteroids were prescribed in 47 of the 49 TBU cases in our study. Concomitant corticosteroids are advocated to limit ocular tissue damage caused by the immune-mediated reaction to *Mtb* bacilli, *Mtb* antigens or retinal antigens.[2,28] Most studies report the use of corticosteroids, together with anti-tubercular medication, in the treatment

Table 4 Multilevel Mixed Effects Model Comparing the HIV-Positive and HIV-Negative Tubercular Uveitis Cases

HIV Positive				HIV Negative		
Multilevel Mixed Effects						
Predictor	**Odds Ratio**	***P*-value**	**95% CI**	**Odds Ratio**	***P*-value**	**95% CI**
Visit (months)						
1.5	1.58	0.805	0.7–1.50	1.16	0.856	0.86–1.19
3	1.12	0.346	0.82–1.7	2.07	0.372	0.42–1.26
6	1.41	0.062	0.84–2.03	1.15	0.093	0.79–1.36
9	1.62	0.008	1.13–2.31	1.25	0.009	1.06–1.48
12	1.59	0.019	1.08–2.34	1.47	<0.001	1.23–1.76
15	1.77	0.003	1.22–2.57	1.52	<0.001	1.29–1.80

Abbreviations: HIV, human immunodeficiency virus; *P*, probability; CI, confidence interval.

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of TBU; however, there is no standardization in the corticosteroid regimen (route, dose and duration).[8,9,12,29] Although the corticosteroid regimen in our study varied, the outcome measured on corticosteroid treatment was standardized; resolution in our study was defined as minimal or no oral corticosteroids (≤10mg) according to the SUN classification.[25]

The resolution of inflammation in the HIV-positive group and the HIV-negative group was achieved at 9 months post-diagnosis. However, there were a small number of cases in the two HIV groups (especially in the HIV-positive group); therefore, these results, although significant, should be treated with caution. To my knowledge, there are no studies comparing resolution or recovery rates between these two groups. This needs to be explored in large prospective multicenter TBU studies. The small proportion of HIV-positive individuals diagnosed with TBU in our study highlights the issue of decreased sensitivity of the TST and QFT-G in immunosuppressed individuals.[30,31] Although a lower (≥5mm) TST measurement corrected for this, it is possible that TBU may have been underdiagnosed in HIV-positive individuals.

There was a higher proportion of TBU cases with chronic uveitis in our study. Chronicity highlights the reluctance of the physicians at our hospital to diagnose TBU and initiate anti-tubercular treatment. Chronicity of uveitis, before anti-tubercular treatment is started, is associated with poor visual outcomes due to complications.[32–34] Thus, a lower threshold for the diagnosis of TBU, and initiation of anti-tubercular treatment to control inflammation and prevent visual-impairing complications at our institution is needed.

Different anatomical classification types of TBU are associated with different treatment outcomes. Depending on the study, higher recurrence of inflammation has been associated with either anterior uveitis, intermediate uveitis or posterior uveitis.[12,20,21] There was a high proportion of TBU cases that had panuveitis in our study, and this may have been due to referral bias from the general clinic to the Uveitis clinic at our hospital; cases with panuveitis and poor visual function may have preferably been referred for specialist assessment. Because of the very small number of cases with the other anatomical classification types, it was not possible to do subgroup analysis comparing resolution between the different anatomical types.

Limitations of the study are: (1) the limited number of cases; (2) the limited follow-up; (3) the missing data in the follow-up visits; and (4) the concomitant corticosteroid-use. (1) The limited number of cases meant that subgroup analyses, such as comparing the different choroiditis types and anatomical phenotypes, was not possible. Although we compared the HIV groups, a meaningful conclusion could not be drawn because of the small number of cases in each group. (2) A longer follow-up would have enabled us to see for how long significant resolution would have been maintained. (3) Although there were missing data in the follow-up visits of the cases in the study, these were addressed by using multiple imputation in the statistical analyses. (4) Although corticosteroids were prescribed in most of the TBU cases, the outcome measure in terms of the resolution of inflammation (on ≤10 mg corticosteroids) was standardized according to the SUN criteria.[25] Strengths of the study are that it is a prospective cohort study where the evaluation of all cases and collection of all the data were done by one Ophthalmologist (HA), and the anti-tubercular treatment regimen and outcome measure were standardized.

Conclusion

Resolution of inflammation in TBU achieved at 6 months suggests that treating these cases with anti-tubercular

treatment for at least 6 months is advisable. Future large prospective cohort studies are needed to compare 6 months to 9 months of anti-tubercular treatment to determine whether stopping treatment at 6 months will maintain resolution. Additionally, large prospective studies are warranted comparing resolution of inflammation between HIV-positive and HIV-negative individuals.

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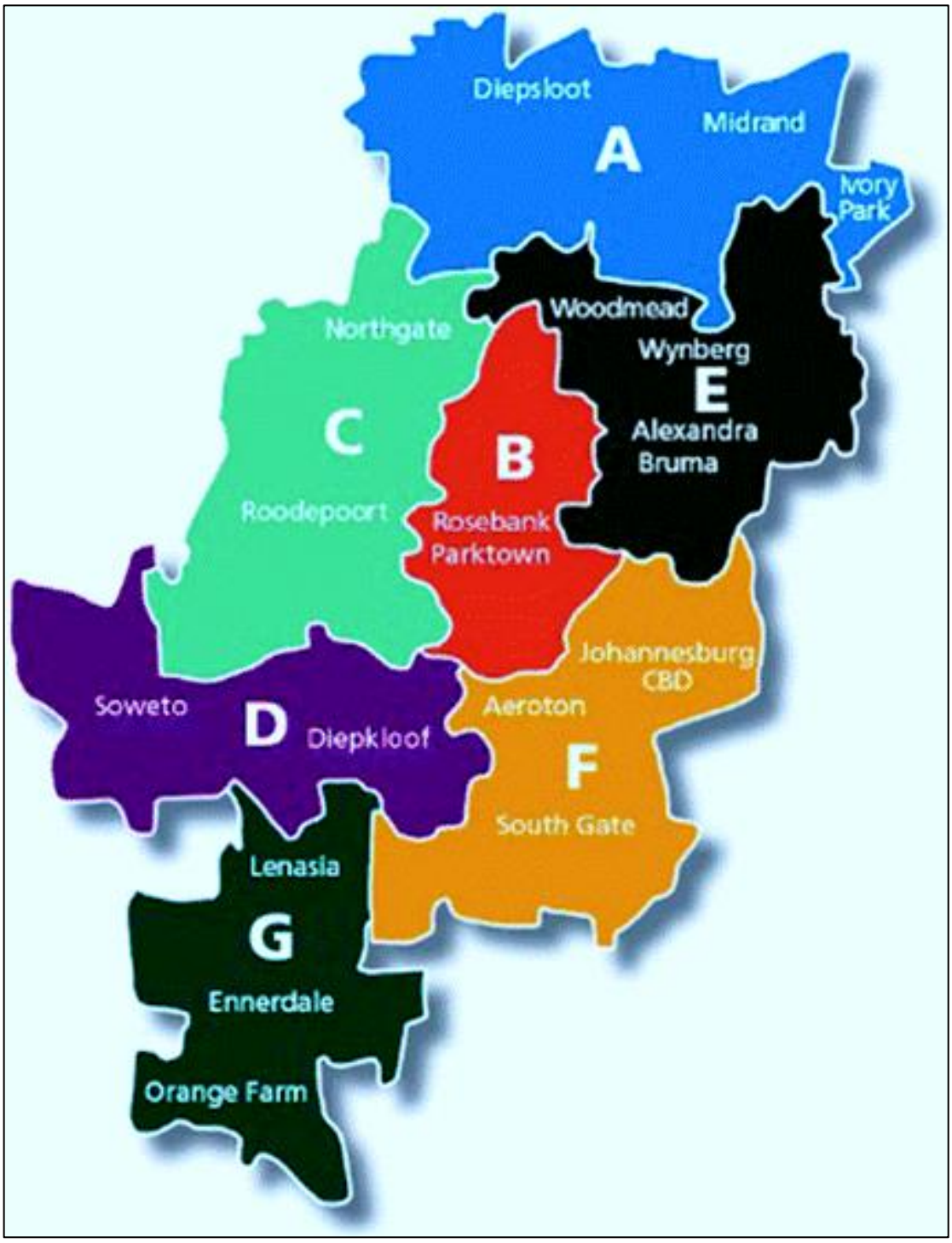
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Appendix 4



Map outlining the sub-districts/regions of the greater Johannesburg Metropolitan area

Appendix 5



Map outlining the six districts of Gauteng Province, South Africa

Appendix 6

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R14/49 Dr Hassan Dawood Alli et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M130942

NAME: (Principal Investigator)	Dr Hassan Dawood Alli et al
DEPARTMENT:	Ophthalmology St John Eye Hospital Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Epidemiology of Uveitis and Diagnosis of Tuberculosis in a Setting of High Human Immunodeficiency Virus (HIV) Prevalence
DATE CONSIDERED:	27/09/2013
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Shabir Madhi
APPROVED BY:	Professor PE Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	25/11/2013

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

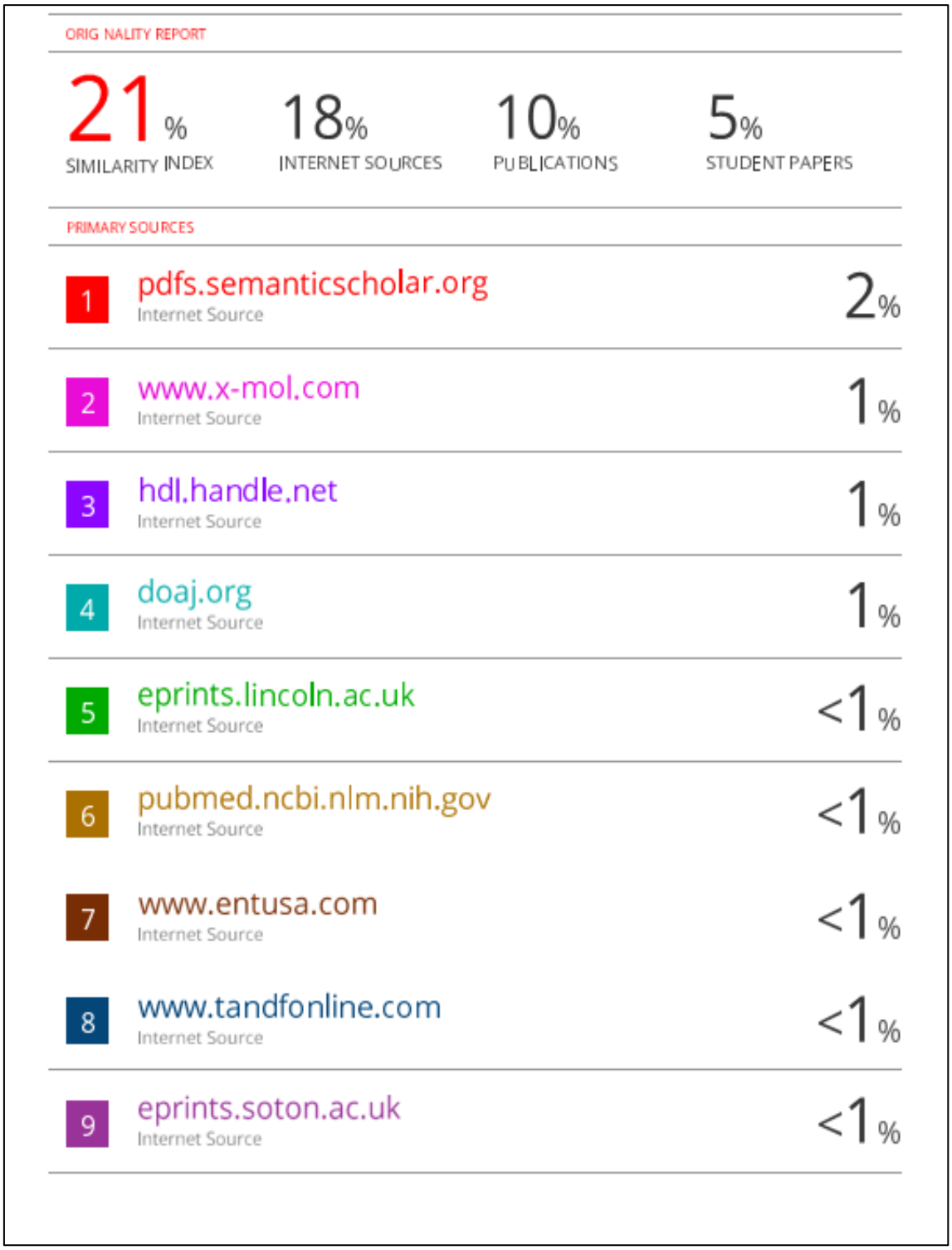
DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature _____ Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix 7



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